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COMMUNICATIONS

PITUITARY EXOPHTHALMOS*

AN ASSESSMENT OF METHODS OF TREATMENT

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EXOPHTHALMIC ophthalmoplegia, progressive or malignant exophthalmos, and thyrotropic exophthalmos are synonyms for the same clinical conditions.

The various terms imply that this bilateral exophthalmos is associated with ophthalmoplegia, that the condition is progressive, leading, if untreated, to grave damage and eventual loss of the eyes, and that it is believed to be due to excess of pituitary thyrotropic hormone.

Sound experimental evidence, such as to make this belief acceptable, has accumulated. Among others, Collip and Anderson (1935), Paulson (1939), Aird (1941), and Dobyns (1946), have been able to produce bilateral exophthalmos experimentally in the guinea-pig by administration of pituitary thyrotropic hormone. The exophthalmos so produced is characterized by its persistence during anaesthesia and after death. It is associated with myopathy of the extra-ocular muscles. It appears more rapidly and is of greater severity in the thyroidectomized animal. It is progressive even after administration of thyrotropic hormone has ceased. In the first three of these characteristics it resembles the spontaneous disease observed in human beings. The clinical features and the pathology of the condition have been fully described by Brain (1936), Naffziger (1931, 1933, 1938, 1948), Mann (1946), and Dobyns (1950). Clinically this condition is distinct from the more common type of exophthalmos associated with Graves' disease. The first symptom is usually a burning sensation and watering of the eye, but not infrequently diplopia is experienced before the patient has become aware of protrusion of the eyeball. More often than not the condition presents as an asymmetrical one, and occasionally it is unilateral in the early stages so that distinction from orbital tumour may cause difficulty. It seems appropriate here to stress that in this variety of exophthalmos, more aptly called proptosis, there is rarely lid retraction. From the onset, the lid space is narrow, rather than enlarged, owing to swelling of the lids. There are heavy bags of oedema below the eyes and there is oedema of the conjunctiva of lids and of globe. The orbital contents, including fat and

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muscles, are oedematous and oedema of the optic disks may be present. The eyeballs protrude progressively, so that lid closure becomes impossible and eventually the eyes protrude beyond the orbit. Corneal ulceration and perforation result. In many cases the condition has made its first appearance shortly after thyroidectomy. The experimental evidence justifies the conclusion that progressive proptosis, localized oedema, and myopathy are due to excess of pituitary thyrotropic hormone, and that their development is favoured by thyroid deficiency, whether due to thyroidectomy or depressed thyroid function from the use of antithyroid drugs (Dobyns and Haines, 1946; Purves and Griesbach, 1949).

These considerations lead to three different lines of therapeutic attack—apart from local surgical measures directed to save the eye when it is endangered by exposure or by papilloedema:

(1) To depress the output of pituitary thyrotropic hormone by administration of thyroid.

(2) To depress the output of thyrotropic hormone by modifying the metabolism of the hormone-producing pituitary cells directly by *x*-radiation without causing lethal damage to the gland*.

(3) To remove surgically a portion of pituitary tissue or destroy it *in situ*†. This therapeutic method would appear unnecessary if it can be shown that less drastic measures hold reasonable certainty of success.

Mann (1946), who reported on eighteen cases, chose the first method of therapy. She recognized the importance of time relationship between different phases of thyroid dysfunction and of excess thyrotropic hormone secretion. The analysis of the clinical histories of her patients led her to distinguish three groups of cases.

(*a*) " Cases of primary thyroid deficiency with compensatory excess thyrotropic hormone secretion ". All four patients in this group were treated with small amounts of thyroid. The result was satisfactory, but only two of the patients showed sufficiently severe ocular signs to convince the reader of the efficacy of thyroid treatment.

(*b*) Ten patients whose histories suggest " initial hyperthyroidism followed by thyroid failure or thyroidectomy with subsequent excess thyrotropic hormone ". Six patients who exhibited progressive proptosis, oedema, and ophthalmoplegia responded well to thyroid medication combined when necessary with local surgical measures such as tarsorrhaphy; one patient recovered spontaneously without ever presenting a severe oedematous syndrome, and two recovered with tarsorrhaphy only, no specific antipituitary treatment being applied.

(*c*) Four cases " in which excess thyroxine and excess thyrotropic hormone

* Analogous attempts to treat acromegaly by a moderate dose of *x*-radiation have been made for many years with excellent results. We have observed several young women suffering from acromegaly whose general health improved after pituitary *x*-radiation; acromegalic features regressed, and visual field defects recovered. Two patients who had been amenorrhoeic for several months returned to a normal menstrual cycle and became pregnant; both were delivered of a healthy baby after a normal pregnancy.

† Dobyns (1950) quotes four cases from the literature where electrocauterization of the pituitary was undertaken simultaneously with unilateral orbital decompression. In all four cases there was retrogression of proptosis and oedema in the eye which had not been decompressed.

arise simultaneously". One of these patients was in a severe thyrotropic state on admission, showing severe oedematous proptosis, papilloedema, and ophthalmoplegia. Bilateral tarsorrhaphy was carried out. His thyrotoxic condition apparently increased and eventually, after a period of rest, he was subjected to *x*-radiation of the pituitary. Several months later eye movements had partly recovered, proptosis, and oedema of lids and optic disk had subsided, visual acuity had returned to normal, and the thyrotoxic state was much improved.

It is this last group of patients which presents the most difficult problem. Thyrotropic hormone is known to be low in blood and urine in acute Graves' disease; it is believed that the hyperactive thyroid depresses pituitary thyrotropic activity. One would have to assume, in cases of simultaneous hyperthyroidism and progressive oedematous exophthalmos with ophthalmoplegia, a thyroid dysfunction different from the hyperthyroidism of Graves' disease; in these cases the hyperactive thyroid fails to exert a depressing effect on the pituitary. Obviously these cases will present the most difficult therapeutic problems. Thyroidectomy and the use of antithyroid substances are contraindicated; such measures might further stimulate the pituitary and increase danger to the eyes. Radiation of the pituitary would appear to be the treatment of choice in these cases combined, when necessary, with local surgical measures to protect the eyes immediately.

In the Edinburgh Department of Surgical Neurology this line of therapeutic approach has been in practice, occasioned by a case that came under observation in 1938.

Case Reports

Case 1. Mrs. P., aged 48, first seen October 25, 1938.—Simultaneous bilateral thyrotropic exophthalmos with mild hyperthyroidism. *X*-radiation of pituitary.

History.—Has been stout since puberty. Six normal pregnancies, now in the menopause. Has shown much fluctuation in weight in the last 3 years but lost altogether 2 st.; still rather plump. Received small doses of thyroid for the last 3 months. Has been jumpy and nervous over the past 2 years. Definite polyuria and polydipsia in the last 3 years, average output 80 oz. in 24 hours. This was not influenced by administration of 1 ml. pituitrin over 7 days. Five months ago patient developed streaming rhinorrhoea with much sneezing; this stopped spontaneously after 3 to 4 weeks and gave way to puffiness of the eyelids. This remained to date. Soon afterwards she developed a corneal ulcer of the right eye which healed after 3 weeks under local treatment, but recurred a few weeks later. Three months ago when oedema of the lids was already marked, patient noticed protrusion of the eyeballs, no diplopia.

Examination.—Patient was found to be overweight. Height 4 ft. 8½ in., weight 10 st. ½ lb. Mild hyperthyroidism, temperature normal, pulse rate between 80 and 96 in bed, average basal metabolic rate after thyroid had been withdrawn for some time +24 per cent.

Blood pressure 140/86. Blood sugar curve 91, 106, 135, 124, 149; one week later 107, 135, 149, 169, last specimen clotted. No glycosuria.

Ophthalmological Findings.—Moderate bilateral proptosis with puffiness of upper and lower lids, chemosis injection of right sclera, small ulcer on right cornea. Right pupil dilated (atropine treatment); left pupil reacts normally. Slight restriction of all external eye movements. Normal visual acuity, fields, and fundi.

X-Rays of Skull.—Definite enlargement of sella turcica with elongation and thinning of dorsum sellae (Fig. 1). Findings indicative of intrasellar expanding lesion.

FIG. 1.—*X*-ray of skull of Case 1. Note globular sella turcica and elongated dorsum sellae.

Treatment.—Preliminary treatment of hyperthyroidism with Lugol's iodine solution, starting 12 days after admission to hospital, when all investigations had been completed. After 8 days' treatment, basal metabolic rate had dropped to −3 per cent. and continued to remain at an average of −5 per cent. in all subsequent examinations. Under this treatment there was slight improvement of lid oedema, and the corneal ulcer healed. *X*-ray therapy of the pituitary was given from December 1, 1938, to January 30, 1939, a total dose of 5000r. After initial deterioration of the eye condition—a minute ulcer appeared on the left cornea and the right-sided ulcer recurred on the third day of *x*-radiation—slow and steady improvement was observed during the period of radiation. At the conclusion of treatment the ulcers were healed, oedema of lids and proptosis greatly improved and the condition continued to improve over subsequent months.

Follow-up.—This improvement was maintained, the patient's general condition remained satisfactory, her blood sugar curve became normal, as did the fluid intake and output, and nervousness and all signs of hyperthyroidism remained absent.

This case is so far unique. We were unable to find another case of thyrotropic exophthalmos with radiological evidence of pituitary enlargement in the literature. Professor Dott, who had experience of the beneficial effect of *x*-radiation of the pituitary in a considerable number of patients suffering from acromegaly, suggested this treatment for thyrotropic exophthalmos. The result which was achieved without any surgical measures, proved fortunate, so that we adhered to direct attack on the pituitary in all subsequent cases.

Case 2. Mrs. D. E., aged 48, shop assistant, admitted August 9, 1947.—Simultaneous bilateral thyrotropic exophthalmos following thyroidectomy. Bilateral orbital decompression, *x*-radiation of pituitary.

History.—Has never been pregnant; menopause for 2 years. Twelve years ago swelling of throat, palpitations, nervousness, slight exophthalmos; treated with iodine for a short time; improved and remained well and very active at war work. Fifteen months ago symptoms and signs of recurring hyperthyroidism without increase of exophthalmos. Ten months ago thyroidectomy; good recovery, improvement in general health, increase in weight. Six months ago (3½ months after thyroidectomy) eyes began to become more prominent, the left one more so. Since then increase of protrusion, gradual development of puffiness of lids and congestion of the eyes. Up to 6 weeks ago, when lids were sutured, no diplopia, no deterioration of vision. When the lids were opened again, the patient noticed that vision had deteriorated and continued to do so rapidly. No diplopia experienced.

Ophthalmological Findings.—Gross bilateral proptosis, more advanced left side, marked swelling of lids, bilateral chemosis, corneal swelling, and opacity, with moderate degree of conjunctival and corneal injection. Left pupil irregular, larger than right; neither reacts to light. Patient unable to converge; abduction of right eye almost completely absent. All other external eye movements only moderately restricted—not more than may be accounted for by the severe protrusion (Fig. 2).

Vision: right eye, hand movements at ½ m. distance with ease, but vision absent in lower nasal quadrant (?due to partial retinal detachment caused by raised intra-ocular pressure); left eye, hand movements at ½ m. distance with difficulty, field of vision full.

Examination of fundi not possible; no other abnormality found except persistently raised blood pressure between 180 and 190 systolic and 118 and 130 diastolic, with pulse rate of 78 at rest.

Treatment.—Immediate bilateral orbital decompression; in addition left cervical sympathectomy was carried out to help improve the nutrition of the seriously damaged left cornea. Biopsy taken from the external rectus muscle on the left side showed the muscle fibres separated, sometimes by oedema, sometimes individually or in groups by

FIG. 2.—Case 2, on admission.

FIG. 3.—Case 2, on completion of *x*-ray therapy.

FIG. 4.—Case 2, two years after completion of treatment.

young fibrous tissue. Some muscle fibres showed sarcolemnal nuclear increase and oedema. There was marked focal and slight general lymphocytic infiltration. At the conclusion of each decompression the lids were sutured with retaining sutures. On the third day after operation the left tarsorrhaphy appeared to be under tension, and resuturing was required the next day.

Ten days after decompression, *x*-radiation of the pituitary was started; from August 28, 1947, to September 9, 1947, a total dose of 3,500r was given. Three days later the lids could be opened, tension being much less.

Three weeks after decompression, when the course of *x*-radiation was almost at an end, all chemosis had subsided. Visual acuity in the right eye was J1 partly. There was still corneal opacity in the left eye. Eyes closed well, but still showed marked puffiness of the lids.

Follow-up.—Seven weeks after operation, and 4 weeks after completion of *x*-radiation, visual acuity in the right eye was 6/6, left eye 6/36. There was no longer any field defect; no pathological change of the fundi was present. Further progress can be judged from Fig. 3. One year after treatment some puffiness of the lower lids was still present. After another year this too had disappeared (Fig. 4).

Visual acuity in the right eye is now 6/6, left 6/12.

Case 3. Miss N. N., aged 31, midwife (hospital staff), admitted March 16, 1949.—Simultaneous bilateral thyrotropic exophthalmos following thyroidectomy. Bilateral orbital decompression, *x*-radiation of the pituitary.

History.—This previously healthy woman developed irritability, fatigue, and loss of

weight 10 months before admission, and mild exophthalmos 3 months later. She had 4 weeks hospital treatment with 0.2 g. thiouracil daily, and was discharged on 0.1 g. maintenance dose. Four months ago, although feeling better in herself, she noticed that the eyes had become bloodshot and sore; exophthalmos increased, lid closure became impossible. Two months ago, thiouracil was replaced by iodine, and on February 2, 1949, she underwent partial thyroidectomy. After this the eyes deteriorated and the patient noticed blurring of vision; she did not admit diplopia but could read better with one eye closed. On admission general condition was satisfactory, pulse rate 78, systolic murmur at apex. Blood pressure 150/100. Urine normal, *x*-ray of skull normal.

Ophthalmological Findings.—Marked bilateral proptosis, epiphora, moderate chemosis, corneal injection but no ulceration, no opacities. All external eye movements somewhat restricted. Visual acuity in the right eye J6, left J10. Engorgement of retinal veins, nasal disk margins blurred, absence of physiological cup. This early congestion of the disk more marked on the right. Before admission the patient had been given stilboestrol without benefit (Fig. 5).

FIG. 5.—Case 3, on completion of *x*-ray therapy.

FIG. 6.—Case 3, 20 months after completion of treatment.

Treatment.—Immediate bilateral orbital decompression without tarsorrhaphy was carried out. Biopsy of intra-orbital fatty tissue showed focal aggregation of lymphocytes; there were only a few striped muscle fibres in the specimen; 23 days after decompression there was still some chemosis, though owing to decompression the proptosis had much retrogressed. *X*-radiation of the pituitary was started 9 weeks after operation and over 3 weeks a minimum tumour dose of 3,000r was given. During this period condition improved dramatically. Patient was discharged with mild exophthalmos, slight oedema of lower lids, no lid retraction, no impairment of external eye movements. The plica seminularis remained somewhat red and swollen on both sides.

Follow-up.—Six months later the eyes appeared satisfactory; left caruncle still looked a little red and prominent. No proptosis, no chemosis. Visual acuity J1 in each eye. Blood pressure 146/102. One year after operation further cosmetic improvement. Blood pressure varied from 134/92 to 158/104. Patient's general condition excellent, worked full time as midwife. After 20 months general condition satisfactory; no symptoms apart from some increase in menstrual flow (Fig. 6).

Case 4. Mr. W. W., aged 58, civil servant, admitted August 21, 1947.—Bilateral asymmetrical thyrotropic exophthalmos without definite thyroid dysfunction. Bilateral tarsorrhaphy and *x*-radiation of pituitary.

History.—No history of thyroid derangement; 8 months before admission the patient noticed redness and slight protrusion of left eye, preceded by a few twinges of pain in it. This condition remained stationary, until 5 months ago after an illness diagnosed as

influenza redness and protrusion of the right eye suddenly developed, and slowly progressed. The patient developed oedema of conjunctiva, but noticed blurring of vision which advanced rapidly only 2 weeks before admission.

Examination.—Good general condition. Soft swelling of thyroid gland but no other clinical signs of thyroid disturbance. Basal metabolic rate, however, was +46 per cent. Blood pressure 130/90, pulse 76. *X*-rays of skull negative.

Ophthalmological Findings.—Left eye, slight protrusion, slight injection of conjunctiva, slight restriction of outward movement, other external eye movements normal. Pupillary reactions normal, also visual acuity, field, and fundus.

Right eye, severe proptosis, massive oedema of lids and conjunctiva, eye cannot be closed. Profuse watery-purulent discharge. Slight opacity of cornea. Apart from moderately good inward movement all external eye movements absent. Pupil reacted to light. Vision J8. Field and fundus normal.

Treatment.—August 24, 1947, tarsorrhaphy right eye. August 27, 1947, some chemosis appeared on left eye. August 28, 1947, *x*-radiation of pituitary started (Fig. 7). Some stitches of right tarsorrhaphy gave way. September 1, 1947, tarsorrhaphy left eye. September 10,

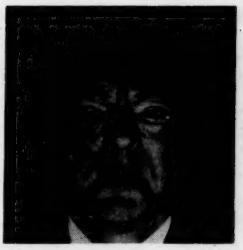

FIG. 7.—Case 4, at beginning of *x*-ray therapy. Note right-sided partial tarsorrhaphy.

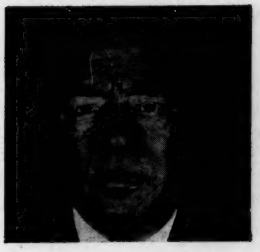

FIG. 8.—Case 4, 2 years after treatment.

1947, both eyes moved fairly well, proptosis subsiding. Some stitches of left tarsorrhaphy cut out to give patient an opening through which he could see; underlying conjunctiva and cornea looked healthy. Lids still puffy. September 18, 1947, *x*-radiation completed, minimal tumour dose 3,500r. September 27, 1947, lids still puffy, proptosis subsided. Patient could read a little with left eye, as tarsorrhaphy was now only partial. October 26, 1947, oedema of lids subsiding.

Follow-up.—July 2, 1948, proptosis and lid oedema very slight but not completely gone; lids to be opened. October 31, 1948, no diplopia, all external and internal eye movements normal; little if any proptosis; still some bagginess of lower lids. December 13, 1949, apart from some bagginess of lower lids and some loss of eyelashes, no ocular abnormality; blood pressure 163/114. April 15, 1951, has remained free from symptoms; blood pressure 170/115 (Fig. 8).

Case 5. Mrs. E. A., aged 50, housewife, admitted August 20, 1947.—Bilateral thyrotropic exophthalmos after thyroidectomy. Evisceration right eye, tarsorrhaphy left eye, *x*-radiation of pituitary.

History.—One sister suffers from exophthalmic goitre. Patient had a soft swelling of the thyroid without symptoms at age 6. Menarche at age 14, periods regular. Four normal pregnancies. Menopause established 4 months ago. Four years ago developed mild symptoms of hyperthyroidism. One year ago these symptoms rapidly increased, with severe dyspnoea and loss of weight. Admitted to hospital on December 13, 1946, in acute state of thyrotoxicosis. Basal metabolic rate +114 per cent. There was then

mild exophthalmos with lid retraction, but no lid oedema. Treated with rest and thiouracil for one month without benefit. During this period 28 blood pressure readings, all taken during strict rest in bed, varied between 140/80 and 188/114, pulse rate between 86 and 104. On January 31, 1947, thyroidectomy was performed; she was discharged barely 3 weeks later in good condition. Basal metabolic rate +14 per cent. She began to put on weight. No noticeable change in the appearance of the eyes.

When she was admitted to the Eye Department on August 20, 1947, she stated that in the first 2 months after thyroidectomy she had gained 2 st. in weight; 3 months after thyroidectomy her eyes became slightly "inflamed", and this progressed over the subsequent 3 months, and marked protrusion and swelling of the lids developed, so that she became unable to close the eyes. A few weeks before admission to the Eye Department vision in the right eye became dim, no diplopia.

Ophthalmological Findings.—Right eye, severe proptosis, chemosis, exposure keratitis with corneal abscess; left eye, proptosis with lid oedema, chemosis, cornea clear but exposed in sleep.

Treatment.—August 23, 1947, evisceration right eye. August 29, 1947 tarsorrhaphy, left eye, leaving medial third of lid space open. September 7, 1947, oedema of lids and right conjunctiva tarsi increasing. September 11, 1947, *x*-radiation of pituitary started; in 3 weeks minimum tumour dose of 3,000r delivered. Three weeks after completion of this treatment redundant conjunctival tissue from the right orbit was excised and a tarsorrhaphy carried out. A month later the orbital oedema was much less but there was still some left-sided proptosis.

Follow-up.—General condition subjectively excellent 13 months later. Patient had worked hard in house and on the farm; she looked well, but exhibited a blood pressure of 190/120, pulse rate 96. The artificial eye fitted well. No oedema of lids. When the left tarsorrhaphy was undone normal conjunctiva and cornea presented. No proptosis, outward movement moderately restricted, all other movements, fundus and vision normal.

Case 6. Mr. A. A., aged 36, motor-bus wheel fitter, first reported September 12, 1946.—Mild bilateral thyrotropic exophthalmos without thyroid dysfunction. *X*-radiation of pituitary.

History.—No symptoms of thyroid dysfunction. Two months ago noticed drooping of left upper lid, 1 month ago developed vertical diplopia, 6 weeks ago noticed puffiness of left eye.

Examination.—General condition satisfactory, pulse rate 84. Blood pressure 136/94.

Ophthalmological Findings.—Moderate proptosis, lid oedema, and chemosis left eye, slight proptosis without oedema right eye. Moderate restriction of upward and downward movement, severe defect of inward movement left eye. Slight drooping of upper lid. Normal external eye movements right eye. Pupillary reactions, vision, and fundi normal both eyes. *X*-rays skull normal. Diagnosis of early thyrotropic exophthalmos.

Treatment.—*X*-radiation of pituitary started on December 4, 1946; total minimum tumour dose of 3,000r delivered.

Follow-up.—Both eyes appeared normal 6 months later; no puffiness of lids; no impairment of external eye movements. Subjectively no diplopia. General condition very satisfactory. Blood pressure 140/95.

Case 7. Mr. R. W., aged 53, shale miner, first reported May 21, 1946.—Early bilateral asymmetrical thyrotropic exophthalmos with doubtful hyperthyroidism. *X*-radiation of pituitary.

History.—Ten weeks ago struck across left eye by piece of shale. No discomfort at the time, but 7 weeks ago noticed slight prominence of left eye. This has fluctuated in severity since. Vertical diplopia for a few days.

Examination.—General condition satisfactory. Pulse rate 76. Blood pressure 158/90.

Ophthalmological Findings.—Moderate proptosis left eye, very slight proptosis right eye. Slight puffiness of upper lid and chemosis at outer canthus left eye. Deficient upward movement left eye. Vision, fundi, fields normal. *X*-ray of skull normal.

One month later the patient reported back and stated that the degree of proptosis was very variable. Sometimes the right, sometimes the left eye was the more prominent. Now upward movement of left eye was almost absent and outward movement deficient. Complained of constant diplopia, but otherwise no change. July 11, 1946, admitted for full investigation and treatment. Eye condition unchanged. Mild clinical signs of hyperthyroidism. Basal metabolic rate +49 per cent.; 3 days later, after 3 gr. nembutal, +20 per cent.

Treatment.—*X*-ray therapy of pituitary from July 22, 1946, to August 8, 1946, total minimum tumour dose 3,500r. Four months later he still showed great variability in the size of the left lid space, amounting sometimes to a definite droop of the upper lid, sometimes to active lid retraction. No other abnormalities found.

Follow-up.—The patient has been followed-up for over 4 years; he has lost all symptoms and signs of hyperthyroidism, and works steadily in the mines. There has been no change in the eye condition; he has adjusted to the diplopia which can still be elicited, but which he apparently spontaneously suppresses.

Case 8. Miss M. B., aged 48, home duties, admitted October 15, 1943.—Mild bilateral thyrotropic exophthalmos twelve years after thyroidectomy. *X*-radiation of pituitary and thyroid medication.

History.—Brother and sister suffered from hyperthyroidism. She was a healthy woman, normal periods throughout reproductive life. Menopause established 6 months ago. Developed tachycardia, exophthalmos, and all usual symptoms of hyperthyroidism 13 years ago. Twelve years ago, after partial thyroidectomy, all symptoms disappeared, but right eye always remained a little prominent. Five weeks ago she noticed vertical diplopia with upward gaze and to the right; 2 weeks ago developed puffiness of lower lids.

Examination.—Satisfactory general condition. Blood pressure 120/74. Basal metabolic rate −25 per cent. Fluid intake and output within normal limits.

Ophthalmological Findings.—Slight bilateral proptosis, right 19 mm., left 16 mm. Marked puffiness of eyelids, more on the right. No chemosis. Vertical diplopia in all directions of gaze. Slight restriction of outward movement of right eye, all other external eye movements full. Vision, fields, and fundi normal.

Treatment.—*X*-radiation of pituitary; minimal tumour dose of 3,000r given in 2 weeks. Thyroid 3 gr. daily; after three weeks, when basal metabolic rate was −10 per cent., reduced to 2 gr. daily. Diplopia subsided within a few weeks of beginning of treatment. Exophthalmometer readings never changed and puffiness of lower lids never quite subsided.

Follow-up.—Condition unchanged after 4½ years.

Case 9. Mrs. J. W., aged 48, housewife, first reported May 7, 1946.—Mild asymmetrical thyrotropic exophthalmos with slight hyperthyroidism. *X*-radiation of pituitary.

History.—No previous history of thyroid dysfunction. Periods still fairly regular. For 18 months mild insomnia, for a few months nervousness and rapid fatigue. Two months ago noticed diplopia on looking up.

Examination.—No signs of thyroid dysfunction. *X*-rays of skull negative.

Ophthalmological Findings.—Right eye normal. Left eye shows trace of protrusion and ptosis. Upper lid lags behind in voluntary and automatic elevation and in lid closure. Defect of upward movement. All other movements normal. Pupil, vision, fundus normal. One week later definite puffiness of lids of both eyes, with slight chemosis of left conjunctiva. Upward and outward movements of left eye now deficient. No

increase of proptosis. Defect of movement disproportionate to forward displacement of eyeball and suggests muscular defect.

Admitted July 10, 1946, for further investigation. Apart from persistently raised basal metabolic rate (+42 per cent., +12 per cent., and +47 per cent.), slight tremor of extended fingers and general nervousness, no signs of hyperthyroidism. Diagnosis of thyrotropic ophthalmoplegia with little exophthalmos.

Treatment.—*X*-radiation of pituitary given from July 18, 1946, to August 7, 1946, minimum tumour dose of 3,500r.

Follow-up.—After 6 months general condition good. Patient sleeps better, is less nervous. No trace of lid oedema or chemosis. No proptosis. No improvement in upward and outward movements of left eyeball. After 3 years diplopia remained unchanged. Patient reports that one to two days before menstruation she always exhibits some puffiness of the lids; on one occasion when she reported during menstruation no puffiness of lids and no chemosis could be detected.

Case 10. Mr. E. K., aged 51, watchmaker, first reported February 7, 1951.—Bilateral thyrotropic exophthalmos without thyroid dysfunction. *X*-radiation of pituitary.

History.—No symptoms suggestive of thyroid trouble. He noticed slight protrusion of right eye without widening of the lid space but with some puffiness of the lids 8 months ago. A month or two ago noticed some swelling below left eye. Three months ago first noticed double vision, which has been variable in type, sometimes vertical, sometimes oblique. He does not connect the type of diplopia with the direction of gaze; while first intermittent, diplopia is now contantly present. He has noticed slight deterioration of vision in the right eye.

Examination.—The patient showed no signs of hyperthyroidism. There is an extrapyramidal type of tremor of the head. No other abnormalities. Blood pressure 160/74.

Ophthalmological Findings.—Proptosis right eye, doubtful proptosis left eye (right 27 mm., left 24½ mm.). Oedema of upper and lower lids of right eye, oedema of lower lid of left eye, upper lid being somewhat retracted. Oedema below both eyes. Outward movement of right eye slightly restricted, all other external eye movements full. Deficient downward movement of right upper lid on downward gaze (Stellwag's sign). Pupillary reactions normal. Cornea clear both eyes, conspicuous watering of both eyes. Visual acuity in right eye 6/6 partly, J4; in left eye 6/5, J1. Fields and fundi normal. *X*-rays of skull normal.

Patient admitted March 13, 1951. During a week of investigations in the ward, no raised temperature, pulse rate averages 76.

Laboratory Findings.—Blood chlorides 530 mg. per cent.; basal metabolic rate +2 per cent.; blood cholesterol 260 mg. per cent.; blood sugar curve 90–140–120–60–60–90.

On March 16, 1950, patient developed oedema of both upper lids, and conjunctival injection, right more than left; slight restriction of outward and down-outward movement right eye.

Treatment.—*X*-radiation of pituitary started on April 13, 1951; 3,000r delivered in 3 weeks.

Exophthalmometer Readings.—

Date	*Right Eye*	*Left Eye*
April 13, 1951	31 mm.	27 mm.
April 18, 1951	*27 mm.*	*24 mm.*
April 24, 1951	26 mm.	24 mm.
May 5, 1951	26 mm.	24 mm.

When he was discharged on May 4, 1951, conjunctival injection and oedema of the lids had almost completely subsided. No change in diplopia and external eye movements; vision in the right eye 6/6, J2; left eye 6/6, J.1.

Follow-up.—On May 24, 1951, he reported some improvement in diplopia. The findings were unchanged.

Case 11. Mr. J. S., aged 63, machine operator, admitted February 1, 1945.—Asymmetrical thyrotropic exophthalmos without thyroid dysfunction. Unilateral orbital decompression, *x*-radiation of pituitary.

History.—No symptoms suggestive of thyroid dysfunction; 3 months ago complained of watering of both eyes, this has continued to date; 2 months ago started to see double, and also noticed protrusion of the left eye and that it would not move. Patient has experienced brief attacks of headache behind both eyes.

Examination.—No impairment of general physical condition. Blood pressure 156/90.

Ophthalmological Findings.—Proptosis of left eyeball with downward and inward displacement. Chemosis of left eye. Upward and outward movements practically absent, inward movement slightly defective. Appearance and all movements of right eye normal. No pupillary changes. Vision normal in each eye. Some blurring of nasal disk margin without other signs of congestion in the left eye. *X* rays of skull, sinuses, and optic foramina negative.

In this case the strictly unilateral proptosis without oedema of the lids suggested the presence of an orbital tumour, though the unusual degree of ophthalmoplegia in the presence of only moderate proptosis raised the possibility of exophthalmic ophthalmoplegia, which had so far remained unilateral.

Treatment.—On February 7, 1945, orbital decompression was carried out. Exploration of orbit disclosed no tumour; orbital fat found to be unusually firm and tense, and muscles appeared unduly bulky. Biopsy specimen of muscle showed several areas of lymphocytic infiltration with surrounding granular degeneration of muscle fibres. At the end of the operation tarsorrhaphy was carried out. The patient was discharged 2½ weeks after operation still showing diplopia and defective upward movement of the left eye, but no proptosis, no lid oedema, and no chemosis.

Further Developments.—Three months later patient still complained of diplopia. Right eye normal in appearance and movements satisfactory.

Fifteen months after the orbital decompression he stated that about 4 months after operation the right eye started to protrude and that the degree of protrusion fluctuated (Fig. 9). In spite of troublesome diplopia he had returned to work, doing 12 hours a day. In the past year he had been under the care of an ophthalmic surgeon in his home town, who had arranged for *x*-radiation of the pituitary. He had received a total of 500r in 10 weeks, and now showed proptosis of right eye with puffiness of the upper lid, deficient outward and absent upward movement. No chemosis, no papilloedema. No change in appearance of left eye, which was protected by the decompression and still showed some defect of upward movement. Vision in each eye 6/6.

FIG. 9.—Case 11, 15 months after left orbital decompression and partial tarsorrhaphy, when *x*-ray therapy was started.

Exophthalmometer Reading.—Right eye 23 mm., left eye 15 mm.

Further Treatment.—In consultation with the radiologist it was decided that the *x*-ray treatment so far delivered could not be regarded as an effective dosage. The patient was given a further course of *x*-radiation of the pituitary, a minimal tumour dose of 3,000r was delivered. Halfway through the treatment exophthalmometer readings were unchanged; 2 weeks after completion of treatment exophthalmos had practically disappeared. There was still slight defect of upward movement and diplopia. The left-sided tarsorrhaphy was opened. No further examination was possible, as he was anxious not to lose any time at work and refused to make the journey to Edinburgh.

Follow-up.—Four years later his doctor kindly informed us that the patient (now aged 67) was well, and still regularly at work, and that the condition of the eyes was satisfactory.

Case 12. Mr. P. D., aged 46, warehouseman, admitted June 8, 1943.—Bilateral thyrotropic exophthalmos 8 years after thyroidectomy. Unilateral orbital decompression, *x*-radiation of pituitary.

History.—Symptoms of hyperthyroidism appeared 12 years ago; 8 years ago partial thyroidectomy for primary thyrotoxic goitre. At that time he exhibited bilateral exophthalmos, but this and all other symptoms disappeared soon after operation, and he returned to full work. At routine follow-up 3 years ago no exophthalmos present. Vertical diplopia started 8 months ago; since then the distance between the two images had gradually increased. For the last 3 months he had been aware of increasing protrusion of the right eye. Lately diplopia has no longer worried him, since one image is " so high up, that he does not bother about it ". For years he has had some nocturnal polyuria.

Examination.—General physical condition satisfactory except for blood pressure of 164/102; heart not enlarged; urine normal.

Ophthalmological Findings.—Moderate degree of puffiness of upper and lower lids, more so on the right side. Purplish discoloration of upper lids with small telangiectases. Slight chemosis of lateral portion of right conjunctiva with slight injection. Very gross proptosis of right eyeball, which seems two-thirds outside the orbit, displaced forwards and downwards, and slightly rotated inwards. Slight proptosis left eye (Fig. 10). Right pupil fails to dilate in dim light; pupil is irregular, reacts sluggishly and inextensively to direct and indirect light and convergence. Left pupil normal. Movements of right eye except for inward movement all severely restricted, left eye moves normally. Vision in the right eye 6/60 with central scotoma; left 6/6, normal field. Fundi normal. *X*-rays of skull and optic foramina normal.

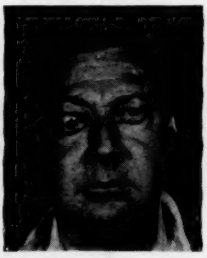

FIG. 10.—Case 12, on admission.

FIG. 11.—Case 12, 15 months after completion of treatment.

It was felt that this was a case of rather asymmetrical bilateral exophthalmic ophthalmoplegia due to excess thyrotropic hormone, exerting its influence in the absence of an efficient thyroid. The central scotoma in the right eye was thought to be due to severe stretch on the retrobulbar portion of the optic nerve.

Treatment.—In order to preserve and restore vision, decompression of the right orbit was carried out on June 14, 1943. At the end of the operation the right eye protruded only a little more than the left. Severe oedema was present for the first five post-operative days. Subsequently retraction of the right upper lid was marked, giving the eye a more exophthalmic appearance than the actual proptosis accounted for. On the 11th day

all external eye movements were free, but the upper lid remained retracted. Vision unchanged, with central scotoma. *X*-radiation of the pituitary started on the 20th post-operative day, completed in 10 days; a minimum tumour dose of 3,000r was delivered.

Follow-up.—Fifteen months after completion of treatment, both eyes still somewhat proptosed, the left, which had not been decompressed, distinctly more so. No puffiness of lids, no oedema of conjunctiva. Both eyes showed deficient outward movement, and the right some defect in upward movement, being still somewhat displaced downwards. Pupillary reactions normal. Vision in both eyes 6/6 with normal fields (Fig. 11).

Fundi showed the appearances of first degree hypertensive retinopathy. He reported symptoms suggestive of hypertensive encephalopathy. These gradually increased. He died from malignant hypertension 3 years after he had first been seen.

Discussion

In all twelve cases the final result was wholly or reasonably satisfactory; no patient showed further progression of the malady after radiation treatment.

For critical assessment of the efficacy of *x*-radiation of the pituitary, those cases are obviously of most value where no local surgical measures were required and where the history suggests steady progress of the malady up to the time that *x*-radiation was started.

Dobyns (1946, 1950) found in the literature 37 cases where *x*-radiation of the pituitary was given; in thirteen the result was satisfactory. He advises that this method should be further considered.

In our Cases 1, 6, 7, 8, 9, and 10, *x*-radiation was applied without local surgical measures; in Cases 11 and 12 it was preceded by unilateral orbital decompression.

Unequivocal evidence based on personal observation that the malady was progressive until treatment was begun, is available in Cases 1 and 10. In both, oedema, congestion, and proptosis improved dramatically during *x*-radiation; ophthalmoplegia, which was less prominent in these cases, also improved.

In Cases 6, 8, and 9, the history strongly suggests progression of the malady until treatment was started. Case 8 is unsuitable for the evaluation of radiotherapy, which was combined with thyroid administration. The final result in case 6 was excellent; oedema, proptosis, and ophthalmoplegia subsided completely. In case 9, oedema and proptosis subsided, while ophthalmoplegia, which had preceded the onset of proptosis, remained unaltered. It is noteworthy that in this case hyperthyroidism also derived benefit from radiation of the pituitary. With the most rigid standard of assessment it can be stated that four patients out of seven were dramatically improved by radiation and that the remaining three were also improved; though it cannot be said with certainty that *x*-radiation was solely responsible for the improvement in the last three.

The record of Case 11 is the most instructive one in our series. Here we have unequivocal evidence that the malady continued to progress after

unilateral orbital decompression, causing the other eye to proptose considerably during subsequent months. There is no reason to believe that spontaneous arrest of the disease process happened to occur just at the time when the patient underwent *x*-radiation.

In Case 12, *x*-radiation was applied within a month of decompression of the more proptosed right eye. The left eye did not require decompression thereafter and remained in a satisfactory condition until the patient died from malignant hypertension. Though spontaneous arrest at various stages of the disease is known to have occurred (Naffziger; Dobyns), one feels that in this case where steady progression of signs had been observed until radiation was applied, it is most probable that the arrest of the malady was due to radiation, while the dramatic improvement in appearance and function of the right eye was effected by local surgical measures.

Proptosis is directly caused by oedema of the orbital contents; it is part of the oedematous complex of the syndrome. Swelling of the lids, and infra-orbital tissues, and especially chemosis and papilloedema are also initially the direct result of orbital oedema; as intra-orbital pressure rises, venous drainage becomes difficult and congestion is superimposed on the oedema and can often be seen at the conjunctival and retinal veins.

Visual defect as met with in this syndrome may be due to a variety of lesions: to swelling or ulceration of the cornea, to partial detachment of the retina (Case 2), to severe stretch of the optic nerve (Case 12), or to long-standing papilloedema with subsequent optic atrophy. This last possibility is rather theoretical; if orbital oedema which is sufficiently severe to cause papilloedema remains unrelieved, the eye will be lost before optic atrophy has developed. Visual defect may, of course, be due to more than one such lesion, all of which are ultimately due to severe oedema in the orbit.

Interference with eye movements may also depend on various mechanisms. If the eye is pushed forwards by a firm mass behind it, its movements may become restricted from purely mechanical causes, though the muscles are still capable of normal contraction. On the other hand, muscle function may be impaired by oedema between the muscle fibres and by lymphocytic infiltration and granular degeneration of muscle fibres. This myopathy is characteristic of thyrotropic exophthalmos, and is not dependent on the orbital oedema. Muscular defect may arise with a comparatively mild oedematous complex, and may persist, after treatment, in the absence of oedema, once the muscle fibres have been replaced by fibrotic strands.

Table I shows the effect of treatment on oedema and ophthalmoplegia in all cases, irrespective of methods employed. Table II shows in greater detail the effect of *x*-radiation on the individual eye signs in the five cases where *x*-radiation only was given. Whatever oedematous signs were present before *x*-radiation, these had subsided after it in all five cases. On the

TABLE I

METHODS OF TREATMENT AND FINAL RESULT

Case No.	Sex	Age (yrs)	Local Surgical Treatment	*X*-Radiation	Result
1	F	48	—	+	Full recovery
2	F	48	Bilateral orbital decompression Tarsorrhaphy Sympathectomy	+	Full recovery
3	F	31	Bilateral orbital decompression	+	Full recovery
4	M	58	Bilateral tarsorrhaphy	+	Full recovery
5	F	50	Evisceration right eye Tarsorrhaphy left eye	+	Oedema left eye subsided Some ophthalmoplegia remained
6	M	36	—	+	Full recovery
7	M	53	—	+	Full recovery
8	F	78	—	+ Thyroid	Some oedema remained Ophthalmoplegia recovered
9	F	48	—	+	Ophthalmoplegia remained Oedema and proptosis recovered
10	M	51	—	+	Proptosis and oedema subsided Ophthalmoplegia improved
11	M	63	Unilateral orbital decompression	+	Proptosis and oedema recovered Ophthalmoplegia remained
12	M	46	Unilateral orbital decompression	+	Practically full recovery

TABLE II

RESPONSE OF INDIVIDUAL OCULAR SIGNS TO *X*-RADIATION

Case No.		Proptosis	Chemosis	Lid Oedema	Infra-orbital Oedema	Papill-oedema	Visual Defect	Ophthal-moplegia
1	Before treatment	+	+	+	+	—	slight	—
	After treatment	—	—	—	—	—	—	—
6	Before treatment	+	+	+	+	—	—	+
	After treatment	—	—	—	—	—	—	—
7	Before treatment	+	slight	—	—	—	—	+
	After treatment	—	—	—	—	—	—	+
9	Before treatment	+	+	+	+	—	—	+
	After treatment	—	—	—	—	—	—	+
10	Before treatment	+	+	+	+	—	slight	+
	After treatment	—	—	—	slight	—	—	slight

other hand, ophthalmoplegia disappeared in one case only, and improved in another case, but persisted in three cases. We have not included Case 8 in this analysis; this patient received thyroid in addition to *x*-radiation, and is the only one in our series who showed persistence of oedematous features when ophthalmoplegia subsided.

The aim of orbital decompression is to relieve oedema and congestion in the orbit and thereby to restore adequate drainage of the extra-orbital tissues as well.

Table III shows the response of the individual ocular signs to orbital decompression and *x*-radiation; special attention is paid to a change of signs in the interval between decompression and *x*-radiation. This interval was long enough in only two cases to justify the statement that improvement was accelerated by *x*-radiation.

The analysis shows that ophthalmoplegia will persist in certain cases whatever method of treatment be adopted. As the defective movements

TABLE III

RESPONSE OF OCULAR SIGNS TO ORBITAL DECOMPRESSION AND *X*-RADIATION

Case No.	Ocular Signs before Decompression		Decompression		Ocular Signs after Decompression		Interval between Decompression and *X*-radiation	Ocular Signs after *X*-radiation	
	Left	Right	Left	Right	Left	Right		Left	Right
2	Gross proptosis Chemosis Corneal opacity Severe visual loss Ophthalmoplegia	Proptosis Chemosis Corneal opacity Severe visual loss Ophthalmoplegia	+	+	Initial increase of oedema	Little change	10 days	Oedema and proptosis subsiding Corneal opacity slowly subsiding Vision improving No ophthalmoplegia	All signs subsiding rapidly Vision normal
3	Proptosis Chemosis Papilloedema Visual loss slight Ophthalmoplegia	Proptosis Chemosis Slight papilloedema Visual loss slight Ophthalmoplegia	+	+	Still some	chemosis	63 days	No abnormality	
11	Proptosis Chemosis Slight congestion of disk Severe ophthalmoplegia	No abnormality	+	–	Severe ophthalmoplegia	Proptosis Slight oedema of lids Severe ophthalmoplegia	16 months	Ophthalmoplegia	Some ophthalmoplegia
12	Slight proptosis	Gross proptosis Chemosis Visual loss Ophthalmoplegia	–	+	Slight proptosis	Visual loss unchanged All other signs subsided	20 days	Slight proptosis Slight ophthalmoplegia	Doubtful proptosis Slight ophthalmoplegia

result from irreversible changes in the muscles, the duration of diplopia and the severity of muscular defect before treatment will be of prognostic significance.

Table IV shows the relationship between the duration and severity of ophthalmoplegia and the recovery of ocular movements.

TABLE IV

RELATIONSHIP BETWEEN DURATION AND SEVERITY OF OPHTHALMOPLEGIA AND RECOVERY OF OCULAR MOVEMENTS

Case No.	Predominant Feature of Syndrome	Duration of Illness	Duration of Diplopia	Degree of Ophthalmoplegia	Recovery of Eye Movements
1	Oedema	4 months	None experienced	Slight	Full
2	Oedema	6 months	None experienced	Severe	Full
3	Oedema	4 weeks	None experienced	Slight	Full
4	Oedema	8 months	None experienced	Slight	Full
5	Oedema	4 months	None experienced	Slight	Almost full
6	None	2 months	1 month	Severe	Full
7	Ophthalmoplegia	10 weeks	5 to 6 weeks	Severe	Little, if any
8	Ophthalmoplegia	5 weeks	5 weeks	Slight	Full
9	Ophthalmoplegia	2 months	2 months	Severe	None
10	None	8 months	3 months	Moderate	Little
11	None	3 months	2 months	Severe	Little
12	None	8 months	8 months	Severe	Little, if any

Seven of the twelve patients showed absence of ophthalmoplegia after treatment; in five, oedematous features dominated the clinical picture, and the fact that they did not experience diplopia before loss of vision makes it certain that ophthalmoplegia, though in several instances severe at the time of admission, must have been a recent development.

It would appear that this malady may take either a very acute course, when congestive features dominate, or a subacute course, when congestive features and ophthalmoplegia are of equal severity or ophthalmoplegia dominates. In these cases, we find weakness of individual eye movements rather than fixation of the eyeball from purely mechanical causes. Early myopathy with irreversible muscular changes appears to be characteristic of the subacute form.

Orbital decompression will not, as a rule, be applied in the less acute cases. This operation is reserved for patients who show rapidly increasing

congestive changes with oedema of the optic disk, or visual defect from stretch of the optic nerve or from retinal detachment.

Damage to the eye from corneal exposure in the severely proptosed eye is avoided by tarsorrhaphy. Tarsorrhaphy alone, however, cannot be expected to remedy rapidly rising intra-orbital pressure. Whenever the eye cannot be adequately closed and there is evidence of further progression of the malady, a combination of orbital decompression with tarsorrhaphy should be employed. In all instances where corneal opacity or ulceration has already occurred, cervical sympathectomy should be carried out, as it will accelerate the healing of corneal lesions.

If immediate danger to the eye has been averted by these surgical measures, it is permissible—and indeed desirable—to observe the patient for a reasonable period without further treatment. Such observation should answer the question how often this malady remains stationary or regresses once the severe congestive phase has been reached. An expectant attitude after local surgical measures will provide an opportunity to study these cases fully and to obtain important biochemical data. If improvement is unduly slow or individual signs (tension under the tarsorrhaphy, ophthalmoplegia after decompression) increase, *x*-radiation of the pituitary should be initiated and biochemical tests should be repeated after a reasonable interval.

In the less acute cases where no local surgical measures are required but where there is evidence of progression of the malady, we believe that *x*-radiation of the pituitary should be applied as soon as full clinical and biochemical data have been obtained.

In this series, the number of patients showing hyperthyroidism associated with pituitary exophthalmos is small. Of the four patients who exhibited a significantly raised basal metabolic rate, only two had clinical symptoms of hyperthyroidism. These two patients improved in their general health after *x*-radiation of the pituitary. The patient who exhibited a severe thyrotoxic state arising simultaneously with pituitary exophthalmos (Mann, 1946), showed dramatic improvement both in general health and in the local condition following pituitary *x*-radiation. Further observations are needed in cases of hyperthyroidism complicated by the oedematous type of exophthalmos. Thyroidectomy as the first therapeutic measure is obviously contraindicated, as is also the administration of antithyroid substances. Both measures must be expected to stimulate the pituitary to increased output of thyrotropic hormone. It is likely that these cases would respond well to pituitary *x*-radiation which should benefit general thyrotoxic symptoms as well as the ocular changes.

Six of our patients (50 per cent.) were females; of these, three developed the malady with the menopause, and two others were approaching the menopause. One of our patients, and several whose records are quoted in the literature (Dobyns, Mann), received oestrogenic substances without benefit to the exophthalmos. The relationship between this pituitary

dysfunction and gonadotrophic pituitary function is a subject for further study.

Summary

The clinical records of twelve patients suffering from exophthalmos of pituitary origin are presented. The effect of pituitary *x*-radiation on this malady is assessed. The indications for *x*-ray therapy and local surgical measures are discussed.

It is a pleasure to record my thanks to Professor N. M. Dott and to my colleagues in the Neurosurgical and Eye Departments of the Royal Infirmary, Edinburgh, for their co-operation, to Professor R. M. McWhirter, under whose direction the patients received radio-therapy, to the Biochemical Department for laboratory data, and to the Department of Neuropathology for histological data.

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PROPTOSIS CAUSED BY LIPOIDOSIS*

BY

AHMAD BEY HANDOUSA

AMONG cases of proptosis, I have met with three in which the causative lesion proved to be a form of lipoid granulomatosis, also known as lipoidosis and xanthomatosis. Two of these cases will be presented in this paper; in the third (Handousa, 1949) the lesion was mainly manifested in the temporal bones simulating double mastoiditis.

The term lipoidosis covers several clinically distinguishable entities of disease resulting from disturbed fat metabolism. Three main varieties are usually described: Gaucher's disease, Niemann-Pick's disease, and Hand-Christian-Schüller disease. They have the common feature of storage of lipoid material in large cells derived from the reticulo-endothelial system. These cells are histologically characteristic and sufficiently diagnostic of lipoidosis. The type of lipoid stored differs in each entity. Kerasin is the main lipoid in Gaucher's disease, phosphatide in Niemann-Pick's disease, and cholesterol and its esters in Hand-Christian-Schüller disease.

Proptosis caused by lipoidosis is very rare and is usually one of the manifestations which may occur early or late in Hand-Christian-Schüller disease. Granulomatous masses forming at the base of the skull in this disease commonly spread and invade the orbit, pressing on the pituitary body and neighbouring structures, thus giving rise to exophthalmos, diabetes insipidus, etc. (MacCormac, 1938). In the case previously published (Handousa, 1949) the lipoid infiltration was a generalized process in which the orbital involvement was late.

The possibility of a localized process of lipoidosis in the soft tissues of the orbit without any skeletal, visceral, or skin manifestations is demonstrated by the two cases here presented.

Case Reports

Case 1. S. S., male, aged 40 (Fig. 1), complained of right proptosis of about 2 years' duration, gradually and slowly increasing without any pain, headache, or change in vision. No history of trauma or syphilis. No diplopia.

Examination.—The right globe was bulging forwards and slightly downwards with limitation of upward movements. Conjunctiva clear; vision in the right eye 6/6.

* Received for publication July 19, 1951.

Palpation revealed a cystic swelling lying in relation to the roof of the orbit and extending above the eyeball from the medial to the lateral side, with the tendon of the superior oblique muscle stretched anterior to it. At the outer limit of the swelling, the orbital edge was irregularly thickened.

FIG. 1.—Case 1, right proptosis caused by a localized xanthomatous mass.

The left eyeball also appeared slightly proptosed, but there was no palpable swelling in the orbit and no limitation of ocular movement. Vision in the left eye 6/6. Fields of vision normal. Nose and sinuses showed no related abnormality.

Laboratory Findings.—Wassermann reaction negative; basal metabolic rate −17 per cent. Urine and stools normal. General clinical examination revealed no abnormality.

Blood:

Total red-cell count 5,100,000, haemoglobin 92 per cent.

Total leucocyte count 4.200 (polymorphs 46 per cent., lymphocytes 42 per cent., monocytes 10 per cent., eosinophils 2 per cent.).

Radiological Examination.—This revealed a large defect in the orbital roof (Figs 2 and 3). No other bony lesion was discovered in the skull or other bones.

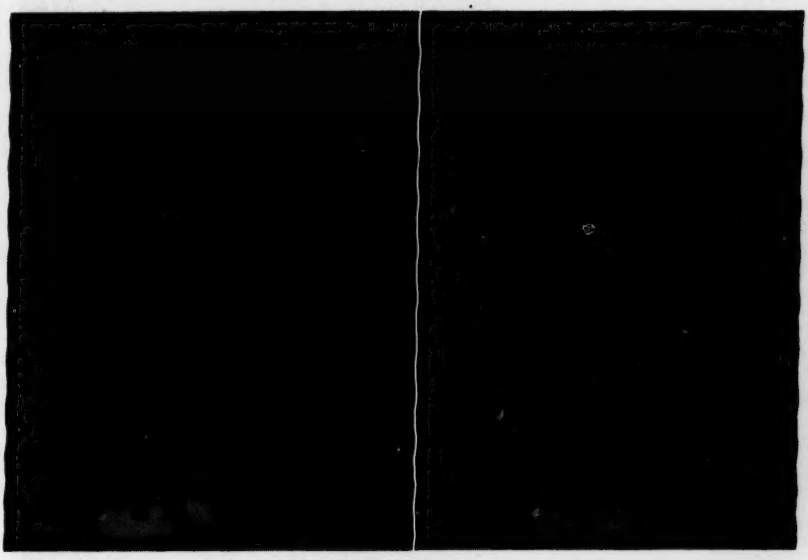
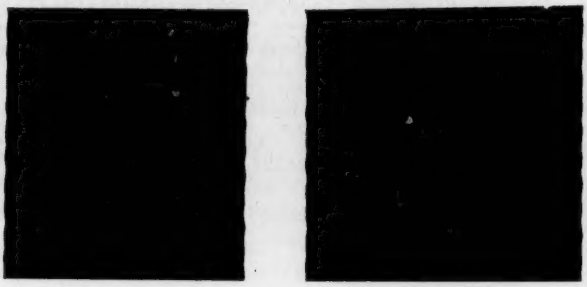


FIG. 2.—Case 1, radiograph of right orbit, showing ? defect in bony roof.

FIG. 3.—Case 1, radiograph of left orbit (cf. Fig. 2).

Exploration revealed the apparent defect on the right side to be merely an upward bulge in the orbital roof forming the bed of the mass.

Exploration.—A fairly large but localized soft mass was found mainly in relation to the outer part of the orbital roof. It was adherent to the mass of the muscle cone with the tendon of the superior oblique muscle spread anterior to it. It could be dissected out completely. No trace of the lacrimal gland was found. The part of the orbital roof forming the bed of the mass was pushed up intra-cranially, but was still intact, and the bone surrounding this bed was irregularly thickened. Figs 4 and 5 give a diagrammatic representation of the position of the mass in the orbit.



FIGS 4 and 5.—Case 1, diagrammatic representations of xanthomatous masses *in situ.*

On section, the cut surface of the mass was dark brown in colour and the fluid which oozed out was full of minute shining particles which proved to be cholestrin crystals.

Histological Examination.—The mass proved to be xanthomatous in nature (Fig. 6).

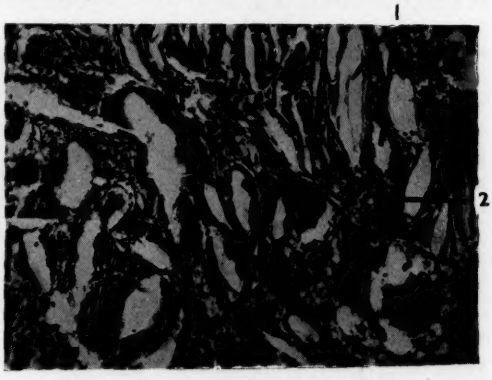


FIG. 6.—Case 1, photomicrograph showing (1) needle-shaped spaces of dissolved cholestrin crystals, and (2) groups of lipoid foam cells.

Follow-up.—The patient had an uninterrupted recovery, and the proptosis has disappeared. He has been seen regularly since the operation (for 7 years) and is in perfect health.

Case 2. H. M. T., boy, aged 4 (Fig, 7), complained of progressive exophthalmos of the left eye of one year's duration, associated during the last month with ptosis of the left upper eyelid.

The condition developed insidiously and painlessly without any fever or constitutional disturbances; the parents state that when one year old the child had ophthalmia which left him with a nebula on the left cornea.

There was no history of trauma or syphilis, and the child had two brothers in good health and free from similar complaints.

Examination.—The left eyeball was proptosed forwards, downwards, and medially, with limited movements in an upward and downward direction, and ptosis of the upper eyelid. The conjunctiva was congested and showed distinct ecchymosis in its lateral part. There was a nebula on the lower part of the left cornea. On palpation, a soft mass could be felt in the upper and outer quadrant of the orbit in the region of the lacrimal fossa. The mass was not tender, and was not adherent to the skin above it; but its extent in depth could not be discovered. The orbital margin was intact all round. The anterior chamber was free and of normal depth; fundus normal.

No abnormality was detected in the right eye, and the neck and pre-auricular regions were free of palpable glands. Except for the presence of adenoids, the nose, nasopharynx, throat, and ears were normal. The general condition was quite good, pulse and temperature were normal. No clinical or radiological abnormality was discovered in the lungs, heart, or abdomen. The size of the liver was within normal limits and the spleen was not palpable. The skin was free of xanthomatous masses.

FIG. 7.—Case 2, left proptosis and ptosis, caused by xanthomatous mass in orbital space.

Laboratory Findings

Urine:

Acid, Sp. gr. 1016.
Albumen-traces.
Pus cells + Red blood corpuscles +.
Bence-Jones reaction—negative.

Blood:

Red-cell count 5,000,000, haemoglobin 90 per cent.
Leucocyte count 12,700 (polymorphs 48 per cent., lymphocytes 43 per cent., monocytes 6 per cent., eosinophils 3 per cent.).
Blood cholesterol 150 mg. Wassermann reaction negative.

Sternal puncture.—Total count 120,000.
(Basophils 10 per cent., staff nucleated 17 per cent., eosinophils 11 per cent., segmented 30 per cent., juveniles 0 per cent., promyelocytes 8 per cent., myeloblasts 8 per cent., lymphocytes 12 per cent., monocytes 4 per cent.).

Radiological Examination.—The left orbit compared with the right was dilated, but its margin was free of erosion. The orbital mass threw a shadow on the orbital cavity covering its upper and outer margins (Fig. 8, overleaf). No radiological lesion was discovered in the flat or long bones.

Exploration.—A large mass, brown in colour, was seen lying between the muscle cone and the orbital wall, extending back almost to the optic foramen and infiltrating all the neighbouring structures. The lacrimal gland could not be made out, but the bony orbital wall looked and felt uneroded. In view of this infiltration I removed only a piece of the mass for biopsy.

Histological Examination.—A mass of lymphoid tissue presenting marked hyperplasia of its reticulo-endothelial cells with numerous groups of large, pale, vaculated, lipoid-laden cells, which gave a mild positive reaction for fat in frozen sections stained by the Sudan III method; the appearances were compatible with lipoid histiocytosis, most probably of the Hand-Christian-Schüller type (Fig. 9, overleaf).

Treatment.—The patient is receiving deep *x*-ray therapy.

DISCUSSION

In these two cases, proptosis was the only complaint and was proved to be caused by a xanthomatous intra-orbital mass.

FIG. 8.—Case 2, radiograph showing primary dilatation of left orbit and shadow of lipoid mass superimposed upon it.

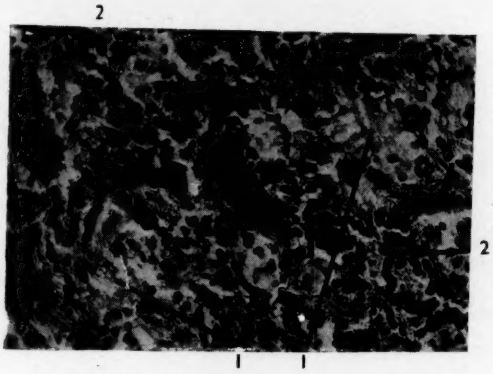


FIG. 9.—Case 2, photomicrograph of section of lipoid mass showing (1) lipoid-laden foam cells, and (2) eosinophil cells.

The mass was large and infiltrative in Case 2, but localized in Case 1. In both cases the mass was found mainly in the upper and outer quadrant of the orbit and the evidence was in favour of origin in the intra-orbital soft tissue. Radiological study, exploration, and histological examination gave

no indication that the mass originated from bone. The lacrimal gland was absent on exploration, having most probably disappeared as a result of pressure atrophy. The serial sections examined histologically did not reveal any evidence of lacrimal gland tissue in the mass. There was no evidence of any similar process of disease in other parts of the body.

Proptosis is one of the manifestations of Hand-Christian-Schüller disease and commonly results from spread to the orbit of the lipoid granulomata forming at the base of the skull. *These two cases demonstrate that proptosis can also be caused by a similar process originating in and limited to the soft tissues of the orbit.*

SUMMARY

Two cases of proptosis caused by a xanthomatous intra-orbital mass are described, and the aetiology is discussed in detail.

I am indebted to Dr. A. Marey, Assistant Professor of Radiology, Professor Omar Bey, Professor of Clinical Pathology, Dr. M. Hashem, Assistant Professor of Pathology, Dr. Ibrahim Mosalem and Dr. Zaghloul for their help in the investigation of these cases and the preparation of this paper.

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PARTIAL TRANSPLANTATION OF THE LEVATOR PALPEBRAE SUPERIORIS IN SUPERIOR RECTUS PALSY*

BY

H. B. STALLARD

London

THE following case report shows that a reasonable result, both functional and cosmetic, may be obtained by the transplantation of the central third of a normally acting levator palpebrae superioris into a completely paralysed superior rectus.

Case Report

J. W., aged 23, had paralysis of the left superior rectus muscle since birth. The left eye was deviated downwards and outwards (Fig. 1), there was complete absence

FIG. 1.—Photograph of deviation of left eye before operation.

of elevation, fixation was eccentric, and there were nystagmoid movements in this eye. There was slight ptosis, the left interpalpebral fissure being 9 mm. at its highest point and the right 10 mm. The action of the levator palpebrae superioris was good. There was marked secondary contracture of the inferior rectus muscle.

Operative intervention was carried out in two stages with a five-week interval between them.

(1) Recession of the inferior rectus 7 mm., which was found to be in tight contracture. Recession of the external rectus to the equator, and resection of 5 mm. of the internal rectus. Fig. 2 shows the result after this operation; the patient is looking up.

(2) Resection of 7 mm. of the paralysed superior rectus and transplantation of the

* Received for publication July 26, 1951.

FIG. 2.—Photograph after first operation. Patient looking up.

central third of the levator palpebrae superioris cut at a site 1 cm. posterior to the upper edge of the tarsal plate and secured with lateral whip stitches of white silk to the upper surface of the resected superior rectus muscle at its insertion. This procedure is illustrated in Fig. 3, which shows also the details of exposure of both the under surface of the levator palpebrae superioris and the superior rectus muscle through an incision in the conjunctiva of the upper fornix. The upper lid is everted over a 'cigarette' roll of gauze and is held thus by two traction sutures in the lid margin. These sutures are clamped to the head towel. The upper margin of the conjunctival incision is held

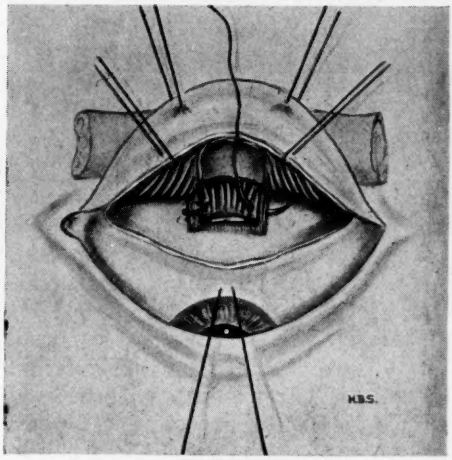

FIG. 3.—Diagram to show transplantation of middle third of levator palpebrae superioris into superior rectus muscle after its resection (second operation).

forwards and upwards by two traction sutures so as to facilitate and increase the exposure of the levator palpebrae superioris and the upper edge of the tarsal plate. A traction suture at 12 o'clock just above the limbus rotates the eye downwards.

To correct the small degree of original ptosis and any impairment of elevation of the lid caused by the transplantation of the central third of the levator, the medial and lateral thirds of this muscle were advanced on to the anterior surface of the tarsal plate.

(*a*)

(*b*)

FIG. 4.—Photographs 6 months after second operation. (*a*) Looking to the front. (*b*) Looking up.

Fig. 4(*a*) and (*b*) shows the result 6 months after operation. The action of the left superior rectus, although not so good as the normal right side, is fair. Cosmetically, the improvement is appreciable.

I should like to thank Mr. P. G. Doyne for his kindness in sending me this patient.

Brit. J. Ophthal. (1952) **36**, 29.

PRELIMINARY REPORT ON THE USE OF METHONIUM COMPOUNDS AND GENERAL ANAESTHESIA IN OPHTHALMIC SURGERY*

BY

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IN his lecture "Medicine, Yesterday and To-morrow", Sir Henry Dale mentioned, as the most recent addition to the technique of preparing a patient for a surgical operation,

> synthetic substances which, by their action on the sympathetic ganglia, lower the arterial blood pressure and enable a postural adjustment of the patient to produce a practically bloodless field of operation (Dale, 1951).

In routine operations on the eyeball, haemorrhage is of no great consequence, since it may be controlled by careful pre-operative preparation, vaso-constrictor drugs, local pressure, or cautery. But in operations which involve accurate technique in small deep cavities amongst important structures, as in the orbit, severe haemorrhage may be difficult to control, and may impede the smooth progress of the operation.

In Plastic Units this situation frequently occurs, since the ophthalmic surgeon is required to deal with the effects of severe trauma and cicatrization in and around the orbit. Such cases do not lend themselves to local anaesthesia as do most operations on the globe, and general anaesthesia has become routine.

Enderby (1950) reported the use of pentamethonium iodide in the production of controlled hypotension during general anaesthesia, but the results were irregular and unpredictable. Since then he has replaced the drug by hexamethonium bromide and made it possible to achieve accurate temporary control of blood pressure in 85 per cent. of his cases.

Rollason (1951) has also found that hexamethonium is more certain and more effective than pentamethonium iodide.

The object of controlled hypotension or "postural ischaemia"† is to eliminate bleeding at the site of operation. This object is achieved by a combination of the effects of hexamethonium bromide on vessel tone with an arrangement of posture which causes re-distribution of blood to the dependent parts of the body.

Enderby and Pelmore (1951) made the following claims for controlled hypotension by this method in general anaesthesia:

(1) Operations can be done more quickly and more easily.
(2) Blood loss is reduced to a minimum where it is often severe.

* Received for publication August 14, 1951.

† Sir Henry Dale's phrase.

(3) Surgical complications such as haematoma and post-operative reactionary oedema are reduced—this is of great advantage in skin graft surgery.

(4) More extensive surgery is possible at one operation when bleeding is no longer a deciding factor.

(5) Post-operative recovery of many patients seems to be improved (see also Rollason, 1951).

Shackleton (1951) later reported further observations on controlled hypotension with methonium compounds and concluded that this was a safe procedure in skilled hands with 75 per cent. good control.

Freeman (1951) suggested that an unexpected failure of hexamethonium hypotension should lead to an investigation of the possible presence of a kidney made ischaemic by local pressure such as might be due to a calcified aneurysm.

Physiology

Paton (1951) has written that the paralysis of autonomic ganglion transmission may be effected in the following ways:

(1) By interference with the release of acetylcholine at the pre-ganglionic nerve endings, as by procaine injections or local calcium deficiency.

(2) By preventing the acetylcholine from acting on the ganglion cell by the use of some inactive drug *i.e.*, " block by competition ". Curare and hexamethonium are examples of such drugs.

(3) By depolarization of the ganglion cell so that it is unaffected by normal acetylcholine, *i.e.*, " block by depolarization ". Nicotine produces such an effect but is always preceded by a period of stimulation.

Paton stresses that a drug which is to be used in therapy for blocking a ganglion must be specific: nicotine, on account of the preliminary period of stimulation, is, therefore, unsuitable for use in man. On the other hand, curare blocks the action of acetylcholine on the ganglia but also causes neuro-muscular paralysis and histamine liberation, with consequent confusion of results when a study of blood pressure is under consideration. Wylie and Churchill-Davidson (1951) feel that further investigation of the side-effects of hexamethonium compounds in man are indicated because of their possible action, in large doses, on the motor end-plates: a resemblance to the depolarizing effect of decamethonium has been noted.

Hexamethonium ($N+(CH_3)_3.(CH_2)_6.N+(CH_3)_3$) is a member of the methonium series of compounds in which the pharmacological activity depends on the number of carbon atoms in the methylene chain joining the terminal quaternary groups. The properties of hexamethonium (C6) are in general those of pentamethonium (C5) and tetramethonium (C4): they have been described in detail by Paton and Zaimis (1951).

In the cat, when the pre-ganglionic nerve is stimulated, contraction of the nictitating membrane, which is served by post-ganglionic fibres, occurs. This preparation has been used by Paton and Zaimis (1951) to assess the effect of ganglionic paralysants. It has been found that hexamethonium will block impulses through the ganglion but that the power of the membrane to contract is still retained as shown by direct injection of adrenaline.

Similarly, post-ganglionic fibre stimulation also remains effective, and it can also be shown that acetylcholine is released and that the ganglion is not depolarized. Paton, therefore, concludes that hexamethonium affects transmission by producing a ganglionic block. Zaimis has found in rabbits that 60 to 70 per cent. of intravenous dose of hexamethonium di-iodide is excreted unchanged in the urine.

In man, hexamethonium influences blood pressure by release of autonomic tone and not by any direct action on the blood vessels; it has no other depressive effect even in large doses and it has no "atropine-like" or adrenolytic action. Paton emphasizes that the depressor effect of acetylcholine and the pressor effect of adrenaline may be markedly exaggerated when hexamethonium is used (see below). Organe, Paton, and Zaimis (1949) established that in man the effects of the drug were similar to those obtained in the cat, and Arnold and Rosenheim (1949) were able to show that pentamethonium lowered the blood pressure and caused warming of the skin of the lower limbs; adrenaline was also still found to be fully effective in its action on the blood vessels. Burt and Graham (1950) confirmed these findings and reported increased blood flow in the lower limbs. Varying results have been reported in the oral treatment of vascular hypertension by hexamethonium but they are outside the scope of this paper. Milne and Oleesky (1951), studying excretion of hexamethonium compounds in man, found that in people with normal renal function most of an intramuscular dose is excreted in the urine, and that caution in use is necessary where poor renal function has been previously established, since there is then a risk of accumulation of the drug in the blood with prolongation of hypotension.

Enderby (1950) suggested that a patient with a systolic blood pressure of 60–70 mm. Hg produced by hexamethonium and appropriate posture was in a suitable state for certain surgical operations, especially where the operation site was elevated, since bleeding was minimal yet tissue oxygenation and respiration were probably fully preserved. The drug does not cause diminished bleeding alone, but only when used in conjunction with a posture which causes blood to be diverted into the lower limbs. The influence of posture has also to be borne in mind when hexamethonium is used in the oral treatment of hypertension.

Paton concludes with the provocative suggestion that methonium compounds may show further specific influences on ganglion synapses according to their carbon chains, *e.g.*, decamethonium acts only on the myoneural junction, whereas pentamethonium and hexamethonium act only on ganglion synapses.

Clinical Applications

It has been stated the object of using the drug in conjunction with posture is to obtain a bloodless field for operation. Arteriolar tone is diminished and the veins fill with blood which is then drained by gravity to the dependent

part of the body: relative ischaemia of the elevated parts of the body is thus produced.

Here the difference in the ischaemia produced by adrenaline must be carefully noted, for it has an important clinical application. With adrenaline the blood clots in the vessel in constriction; the vessel dilates after the effect of the drug has passed off, and this allows the calibre of the vessel to increase, so that the clot may be dislodged by a return of normal blood pressure and a reactionary haemorrhage may occur. With hexamethonium, on the other hand, the vessels clot when dilated; thus subsequent blood pressure changes do not produce reactionary haemorrhage, since there is no increase in calibre of the blood vessel when the effect of the drug wears off: instead there is a return of vessel tone which holds the clot more firmly.

Drops or injections of adrenaline should never be used in conjunction with hexamethonium because of the tendency to obtain exaggerated and dangerous effects. In this connection Burn (1951) points out that adrenaline has a blocking action on the sympathetic ganglia as well as directly on the vessels themselves. Consequently, when the direct vaso-constriction wears off, the ganglion block prevents impulses from the vasomotor centre from reaching the blood vessels, and therefore the blood pressure is not maintained. He suggests that posterior lobe extract of pituitary gland, which has no such block effect on the ganglia, would seem to be the more desirable pressor remedy to use when the blood pressure has fallen low because of the action of hexamethonium. He recommends that it should be administered in such cases as a slow intravenous saline drip containing 10 units pituitary (posterior lobe) extract in each 50 ml. saline.

Technique.—Enderby and Pelmore (1951) described their current technique, which is used as a routine in all our ophthalmic cases selected for general anaesthesia in whom this technique is considered suitable. Intra-tracheal anaesthesia is used with thiopentone as the basal anaesthetic. To assist intubation a muscle-relaxant drug is added as required. Anaesthesia is maintained by nitrous oxide and oxygen (2–1) in a semi-closed circle absorber assisted occasionally by very small doses of ether. Cyclopropane is avoided. The Gordh needle is placed in the most convenient vein on the dorsum of the foot.

Dosage.—The initial dose of hexamethonium varies with age and pre-operative blood pressure. A young adult receives 50 mg. and consecutive blood pressure and pulse readings are taken every 3 minutes. Patients over 40 years receive 30–40 mg.; hypertensives and those over 60 years begin with 20 mg. Young people show an increased pulse rate of 120–140 per minute and the effect of posture is not marked. In older patients, on the other hand, the pulse rate does not increase much but postural influence is more profound. Therefore, in young people more hexamethonium and extreme posture (up to 40° reverse Trendelenberg) may be required, whereas in older patients an initial small dose with a small tilt of 5° to 10° reverse

Trendelenberg is often adequate. The object is to maintain a steady systolic level of 60–70 mm. Hg. If the pressure falls below 50 mm. Hg the tilt is reduced. Shackleton (1951) reports maintenance of hypotension of 60 mm. Hg for 2½ hrs without ill effects during a plastic operation on the scalp.

Precautions.—Enderby and Pelmore stress that all hypotensive patients must have the undivided attention of the anaesthetist, who records consecutive pulse and pressure readings whilst observing the site of operation and regulating the tilt as required. Furthermore, it is very important that there should be a *gradual* reversion to the horizontal position in the recovery period after operation in order to avoid abrupt variations in the blood pressure. The airway must also be most carefully preserved in hypotension cases. Ivor Lewis (1951) also emphasizes the fundamental importance of a clear airway in this technique. He has reported negligible blood loss in 74 thoracic cases where pressure was maintained at 60 mm. Hg, but in six other cases the blood pressure could not be reduced below 90 mm. Hg and there was much greater oozing. Less vomiting was noted and no deleterious effects were encountered in his series.

Similar results are reported by McLoughlin and Watson (1951) in a recent series of 200 plastic operations where low pressure and ischaemia were considered justified on account of the risks of post-operative haematoma formation, serious blood loss, or prolongation of operation time by bleeding, or where a patient had hypertension. They noticed that several patients with a reputation for post-operative vomiting showed an encouraging freedom from this complication. The disadvantages mentioned are the awkward position of the tilted patient and the striking pallor of the skin flaps. Reactionary haemorrhage occurred in two cases, but these workers feel that this will be mitigated in future by improved technique. No serious hazards have been encountered: minor sequelae noted are drowsiness, local venous thrombosis, and anorexia due to reduction in gastric secretion.

Dangers.—Enderby and Pelmore have reported a case where a small reactionary haemorrhage occurred because of an inadequate posture which allowed the blood pressure to rise too quickly after operation. There was post-operative bleeding in two other patients, but in them there were other complicating factors such as disturbance of dressing. In another patient an injection of adrenaline had been given. Vomiting appears to be reduced and occasionally there is temporary disturbance of accommodation after operation. Subject to the precautions stated above, no ill effects have been observed.

Shackleton (1951) lists the following possible dangers in the use of postural hypotension:

(1) Reduction of cerebral circulation below the safe level. In hypertension a sudden reduction could well be dangerous.

(2) An ill effect on the circulation on the kidneys.

(3) Prolongation of hypotension.

(4) Risk in the immediate post-operative stage, especially during transport and lifting into bed.

(5) A failure to establish initial complete hypotension by an inadequate dose.

He states that these dangers are probably mostly theoretical, but emphasizes the need for keeping accurate blood pressure records on return to the ward and for having "Methedrine" (methyl amphetamine hydrochloride—dosage 10 mg.), a potent vaso-constrictor, available as a precaution. He reports a case in which anuria followed the use of the drug and death occurred 2 days after operation. There had been, however, errors of technique in this case, in that the drug was used late to control established haemorrhage instead of at the beginning of the operation to prevent it; there was a possible reduction of blood volume; post-operative hypotension had been allowed to persist too long without correction.

It is essential with this technique to maintain full circulating blood volume and to use an adequate initial dose of the drug to produce an adequate hypotension. Rollason (1951) reports that he has had satisfactory experience and has been much impressed in certain types of operations; he stresses the importance of maintaining blood volume, and avoids vaso-pressors except where the hypotension has been prolonged.

Boyes Korkis (1951) stresses the importance of team-work, and of special attention by the nursing staff to the correct post-operative positioning of the patient in bed. He has found this method of anaesthesia very helpful in major neck surgery, and where the surgeon has to work in a deep dark hole as in external ethmoidectomy.

Use in Ophthalmic Conditions.—It has been our duty to carry out many operations on the orbit in the Plastic Units at East Grinstead and Park Prewett, and we have found this method of anaesthesia to be of great assistance. Such operations include immediate or delayed globe implants of various kinds, especially when associated with large varicose aneurysms of the orbit, cartilage wedge insertions for correction of cyclophoria after middle third facial fractures, reconstruction of the orbit after trauma, rhinostomies of all kinds, neoplasms of the orbit, and different explorations of the orbit. Extensive plastic procedures on the lids, the Blascovicz operation for ptosis, and mucous membrane or skin grafts in socket reconstruction, are much facilitated by the absence of haemorrhage. Our youngest patient was a child aged 3 on whom double cystorhinostomy was performed, and our eldest patient was a hypertensive woman aged 64 who had a large meningioma of the orbit removed after having twice been denied operation on account of the size of the tumour. It is interesting to note that in this patient later a slight blow on the face against a door produced a large haematoma. Both these operations were without incident and bleeding was negligible, and in over one hundred ophthalmic cases we have seen no ill effects. In addition, we have knowledge of over one thousand cases handled by our

colleagues in the Departments of Anaesthesia at the Plastic Units without any serious complications which could be attributed to this method of anaesthesia.

During extensive operations on the orbit which would normally result in considerable haemorrhage, it is uncanny to see no bleeding from the incision; no sucker is necessary and no artery forceps are used when postural hypotension has been established. The detailed dissection of structures is easy and the definition of fine detail in the orbit can be carried out with ease. In rhinostomies, troublesome bone bleeding is eliminated, and accurate suture work at depth is much facilitated. It is unusual for us to have to use more than one or two swabs in extensive operations such as the removal of large orbital tumours. Furthermore, it is our opinion that post-operative fibrosis from haemorrhage, and oedema as the result of manipulation, are much reduced.

Intra-Ocular Pressure.—We feel that this method of anaesthesia might be useful in the treatment of acute glaucoma. As is well known, many such cases respond to treatment by the usual local remedies combined with repeated retrobulbar injections of procaine and alcohol. There are, however, a few stubborn cases in which the intra-ocular pressure remains dangerously and persistently high, so that operation under general anaesthesia is desirable. Some small reduction of the eye pressure can be expected with basal anaesthesia, but when hexamethonium is used the fall in intra-ocular pressure may be considerable, and surgical procedures such as basal iridectomy can be carried out with greater safety.

In the normal eye, it can be demonstrated that the intra-ocular pressure may fall from 25 to 18 mm. Hg under basal anaesthesia, but with postural hypotension the intra-ocular pressure cannot be registered on the Schiötz tonometer and the cornea will remain concave until it is manipulated back into shape.

Much more experience in the application of the drug in this condition is required, but the suggestion is offered in this preliminary report in order that it may be tried by colleagues who may require general anaesthesia in stubborn cases of acute glaucoma.

Discussion

It is our cautious and preliminary opinion that there is a place for the use of hexamethonium compounds in general anaesthesia for ophthalmic surgery.

Ophthalmic operations are accurate procedures which demand exact technique, and any agent which is safe should be used if it adds to the ease and precision of the surgeon's task. The value of an ischaemic field in orthopaedic surgery has long been recognized. With combined hypotension and postural ischaemia, similar benefits are now extended to the ophthalmic field. The operations mentioned above are not impossible without this

agent, but all are rendered easier and more accurate with it. Much more experience is yet required, but in our ophthalmic surgery so far the value of the drug has been unquestionable, and it has reduced many surgical manœuvres of potential difficulty to relative simplicity.

Summary

(1) A bloodless field of operation can be produced by the use of hexamethonium with a suitable posture for operations in and around the orbit where bleeding would impair efficient and accurate surgery. It is a safe procedure in skilled hands.

(2) The undivided attention of a skilled anaesthetist is essential both during the operation and until normal blood pressure has been established on return to bed. Adrenaline in all forms is contraindicated. The blood volume must be maintained.

(3) No serious ill effects have been encountered in our series of ophthalmic cases, nor reported in a series of one thousand cases at the two Plastic Units which we serve.

(4) This method has a definite potential value in the treatment of severe acute glaucoma requiring surgical treatment under general anaesthesia.

(5) Other advantages are that the assistant is freed from the task of maintaining haemostasis, that fewer instruments are employed in a small wound, and that considerable time can be saved.

(6) Blood loss is eliminated, post-operative oedema due to manipulation is reduced, and secondary fibrosis from organized blood clots, especially important in rhinostomies, is avoided.

We acknowledge with gratitude the help and guidance we have received from Dr. Hale Enderby who has been largely responsible for the introduction of this method of anaesthesia. Our thanks are also due to other colleagues in the Departments of Anaesthesia at the Plastic Units at East Grinstead and Park Prewett Hospitals with whom we have the privilege to work.

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Brit. J. Ophthal. (1952) 36, 37.

ANATOMICAL STUDY OF THE RETINAL CIRCULATION*

BY

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THE retinal circulation, and, in particular, the capillaries, have been studied after the injection of Indian ink into the central retinal artery. These researches were undertaken for a double purpose; firstly to verify that the retinal circulation is really terminal, and secondly to see if a horizontal vascular *raphé* exists between the macula and the temporal periphery analogous with that of the nerve fibres; in other words, to ascertain whether the circulation of the superior part of the temporal half of the retina is independent from that of the inferior part.

Our technique is quite simple. After opening the skull and trephining the optic canal, in addition to the globe and the optic nerve (as far as the chiasma), the orbital contents and the perichiasmal tissues are removed, including the fifth bend of the internal carotid. Through this is introduced a fine cannula, which is made to penetrate first into the ophthalmic artery, and then into the central artery of the retina. After irrigation with distilled water, Indian ink is injected very slowly and with an even pressure.

The following conclusions have been reached:

(1) There exists, in the retina, a dense, complex, tortuous, and irregular capillary network. There is clearly distinguishable a superficial net and a deep net which anastomose freely (Fig. 7).

(2) The capillary net is much closer and denser at the posterior pole than at the periphery of the retina (Figs 1, 2, and 3). Its density progressively diminishes from the centre towards the periphery, as do the arterial and venous networks.

(3) Contrary to what is observed in certain animals, for example the rabbit (Fig. 4), the retinal circulation in man is truly terminal (Figs 2 and 3); at the periphery, as at any other area of the retina, no direct communication between an arteriole and a venule may be seen; the junction is effected only through the capillary network.

(4) The circulation in the superior part and that in the inferior part of the temporal half of the retina are not independent. On the contrary, the

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FIG. 1.—Vascular network of the retina at the posterior pole. × 45.

FIG. 2.—Vascular network of the retina at the periphery. × 10.5.

FIG. 3.—Vascular network of the retina at the periphery. × 45.

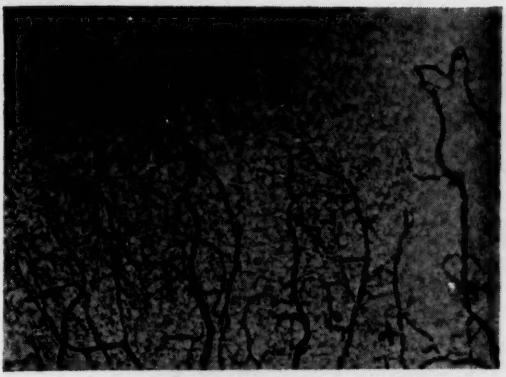

FIG. 4.—Vascular network at retinal periphery in the rabbit.

FIG. 5.—Horizontal *raphé* at level of paramacular region.

FIG. 6.—Horizontal *raphé* between equator and macula.

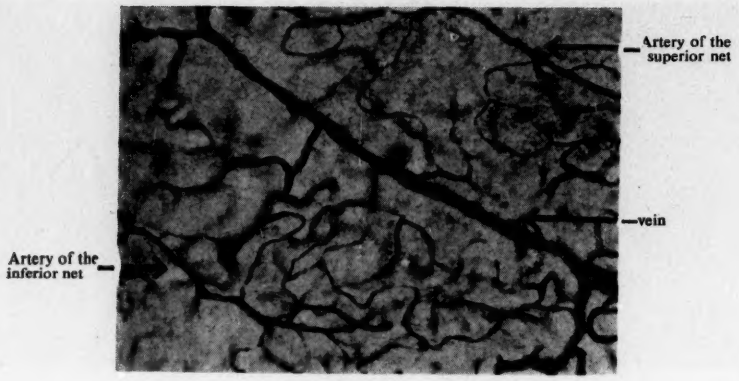

FIG. 7.—Horizontal *raphé* between equator and macular region.

two circulations, the superior and the inferior, anastomose intimately everywhere through a rich capillary network, which is also well marked in the paramacular region (Fig 5) as well as at the more peripheral regions (Figs 5, 6, and 7).

This last point seems to us to be very important, as it suggests that the arcuate scotomata seen in glaucoma are not angioscotomata caused by an arrest of the precapillary circulation, but are, in reality, neuroscotomata.

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CIRCULATION OF THE AQUEOUS HUMOUR AND THE EXPERIMENTAL DETERMINATION OF ITS RATE OF FLOW*

BY

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THE current concept of the physiology of the aqueous humour assumes a continuous circulation (" flow ") of this fluid. From its ultimate source in the plasma, the aqueous humour is regarded as being formed by the diffusion of some of its constituents and the active transport (" secretion ") of others across cellular membranes situated principally in the ciliary body; the fluid so formed then circulates through the posterior and anterior chambers and leaves the eye, largely by drainage through Schlemm's canal, or through its homologue in lower animals.

The evidence for the presence of an aqueous circulation drawn from various sources has been summarized by Friedenwald and Pierce (1932a) and by Sugar (1942). Briefly, it is derived from clinical observations in cases of glaucoma and iris bombé, and from experimental studies, many of them made in the 19th century. Knies (1878) introduced dyes into the vitreous compartment and noted that they quickly found their way into the anterior chamber; similar observations were made by Gifford (1885), Ulbrich (1908), and Abelsdorff and Wessely (1909), among others. Leber (1895a, b) first put forward the hypothesis of a through-and-through aqueous circulation, whereby the aqueous humour escaped from the anterior chamber by filtering through the trabeculum into Schlemm's canal and thence into the intrascleral venous plexus; this assumption was placed on a firmer foundation by the observation of Seidel (1921, 1922) that substances injected into the anterior chamber find their way into the episcleral vessels, and by the more recent discovery by Ascher (1942) of aqueous veins connecting Schlemm's canal and the limbal network with the conjunctival and episcleral veins.

Further support for the existence of a continuous flow of aqueous is derived from the consideration of equilibrium ratios (that is, the ratio of the concentration of a substance in the aqueous to its concentration in the plasma-water when a steady-state has been attained). Non-electrolytes entering the eye by diffusion should accumulate in the anterior chamber until their concentration in the aqueous humour equals that in the plasma-water. The existence of equilibrium values of less than unity is, however, well

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documented; the concentration of urea in the aqueous humour is only 75 per cent of that in the plasma, and there can be no question of the utilization of this compound within the eye such as might be argued to be the explanation of the 15 per cent. deficit of glucose in the aqueous humour. Such a deficit is explicable on the hypothesis of a continuous circulation of aqueous humour and loss of the constituent by flow through Schlemm's canal. Kinsey and Grant (1942b) found that a rate of exit of 1.4 per cent. per minute agreed reasonably well with the curves they derived mathematically from experiments with eight different compounds in rabbits; this implied that all compounds left the anterior chamber at the same rate, a rate which represented the rate of flow.

Methods of Measuring the Rate of Flow

(A) Direct Measurement

From Hovius (1702) onwards, the early workers, who interested themselves in the rate at which the aqueous humour was "secreted", employed direct measurement, usually by cannulation of the anterior chamber and measurement of the quantity of fluid which emerged in a given time, or, using a manometer, by measuring the amount of fluid which had to be fed into the anterior chamber in order to keep the intra-ocular pressure constant. In many of these experiments, enucleated eyes were used. The disturbance to intra-ocular hydrodynamics which accompanies such methods precludes a physiological assessment, but, as they are of interest, some of the results so obtained have been set out in Table I.

A new method was introduced by Uribe y Troncoso (1909), who collected blood from the episcleral veins and estimated the extent to which it had been diluted by the aqueous humour draining into it. Friedenwald and Pierce (1932a) obstructed the normal outflow through Schlemm's canal with serum, and measured the rate of emergence of aqueous humour through a cannula inserted into the anterior chamber when the intra-ocular pressure was kept constant.

A more subtle approach was made by Bárány and Kinsey (1949), who took advantage of the rapid rate of clearance of certain substances by the kidneys after their introduction into the blood. These substances, the contrast media Rayopake and Diodrast, into which radio-active iodine had been introduced, and *p*-amino hippuric acid, were injected (separately) into rabbits, and the plasma concentration maintained high for 2 hours to enable diffusion into the eye to occur. The injection was then stopped and the plasma concentration fell off sharply; the first aqueous sample was removed when the plasma concentration had fallen below the aqueous concentration, and the second an hour later. When due allowance was made for the concentration of the test substance still remaining in the plasma, the value of the rate of exit (k_{out}) could be calculated. Since the substances employed enter the aqueous very slowly, it was assumed that they would also diffuse out very slowly and would so leave the anterior chamber primarily by flow; the calculated value of the rate of exit would thus closely approximate to the value of the rate of flow (k_{flow}).

Fluorescein was employed in a similar manner by Goldmann (1950), who measured its rate of disappearance from the anterior chamber following its intra-

TABLE I

ESTIMATES OF THE RATE OF FLOW OF AQUEOUS HUMOUR
OBTAINED BY DIRECT MEASUREMENT

Method of Direct Measurement	*Reference*	*Animal*	*Rate of Flow (cmm./min.)*
Fluid emerging from anterior chamber	Jesner (1880)	Rabbit	44
	Bentzen (1895)	Rabbit	5–6
	Bellows and Chinn (1940)	Dog	20
Oil in anterior chamber Cannula in vitreous	Leplat (1889)	Rabbit	4
Fluid required to keep intra-ocular pressure constant	Priestley Smith (1888)	Sheep (dead)	26
	Bentzen and Leber (1895)	Human (dead)	4–9
	Niesnamoff (1896)	Rabbit (dead)	7
		Rabbit (living)	1
		Pig (dead)	7
		Dog (dead)	11
		Cat (dead)	24
	Leber and Pilzecker (1906)	Pig (dead)	5–6
	Henderson and Starling (1906)	Cat (dead)	10.8
Outflow from anterior chamber with Schlemm's canal blocked	Friedenwald and Pierce (1932a)	Dog	1
Rate of formation of secondary aqueous	Kronfeld and Lin (1936)	Human	3
Dilution of blood in episcleral veins by admixture with aqueous	Uribe y Troncoso (1909)	Rabbit	2–3

venous injection in human subjects. Another method for the clinical measurement of the rate of flow in the human eye was devised by Grant (1950a), who found that in glaucoma there is not an excessive amount of aqueous formation but an increased resistance to its escape from the anterior chamber, an increased resistance which is detectable by Grant's " tonographic " method in early wide-angle primary glaucoma before the intra-ocular pressure becomes raised (Grant, 1950b).

A method, similar in principle to those of Bárány and Kinsey and of Goldmann, has been devised employing glucose and galactose. The blood level is raised by intravenous injection so that diffusion into the eye can occur. The blood glucose (galactose) level is then lowered by the intravenous injection of insulin, and the rate of disappearance of glucose (galactose) is determined by removing samples of aqueous humour at intervals of one hour. The objection may be raised in the case of glucose that some utilization occurs during the experiment so that the true rate of exit is slower than would appear from the rate of disappearance of glucose. This objection does not hold in the case of galactose, for this substance must be converted to glucose before it can be utilized, and the only known sites of such conversion are the liver, kidneys, and intestinal tract (Bollman, Mann, and Power, 1935). Table II (overleaf) summarizes the results obtained by various authors using this type of experimental method.

Determination of Rates of Exit of Glucose and Galactose

Method.—Rabbits weighing 2.0–2.2 kg. were used under pentobarbitone sodium anaesthesia, except in two experiments in which general anaesthesia was not employed.

TABLE II

RATE OF FLOW OF AQUEOUS HUMOUR DETERMINED BY THE RATE OF DISAPPEARANCE OF VARIOUS SUBSTANCES FROM THE ANTERIOR CHAMBER

Reference	Animal	Substance	Rate of Flow (per cent. per min.)
Bárány and Kinsey (1949) ...	Rabbit	*p*-amino hippuric acid	1·43
		rayopake	1·25
		diodrast	1·22
Goldmann (1950)	Human	fluorescein	1·1
Davson and Matchett (1951)	Rabbit	*p*-amino hippuric acid	0·97
Bárány (1951)	Chicken	*p*-amino hippuric acid	1·7—2·0
Present paper	Rabbit	glucose	1·58
		galactose	1·03

The blood level was raised by the intravenous injection of 20 ml. 5 per cent. glucose or galactose. 30 min. later a further 5 ml. were given intravenously. After one hour, 10 units of soluble insulin were given intravenously, and thereafter blood samples were taken at 10-min. intervals until the end of the experiment; the first aqueous sample was removed 45 min. after giving the insulin, and the second sample 60 min. after the first. Glucose was estimated by the method of Somogyi (1945), and galactose by the same method after the glucose had been removed by yeast fermentation.

Results.—The determinations of the rate of disappearance of glucose and galactose are presented in Table III. The mean rate of disappearance of glucose is 1.58×10^{-2} min.$^{-1}$ (*i.e.* 1.58 per cent. per min.). This does not correspond to the rate of flow, since some glucose in the anterior chamber will be metabolized during the experiment, particularly by the lens, but since the amounts of glucose contributed to lens metabolism by the aqueous and vitreous respectively are not known, allowance for the amount of glucose lost by metabolism cannot be made.

TABLE III

RATE OF DISAPPEARANCE OF GLUCOSE AND OF GALACTOSE FROM ANTERIOR CHAMBER OF RABBITS CALCULATED AS

$$k_{out} = \frac{r}{t_2 - t_1} \ln\left(\frac{C_{a_2} - rC_2}{C_{a_1} - rC_1}\right)$$

Glucose	Galactose
2·22	1·16
1·58	0·94
2·62	0·65
1·48	0·95
1·16	1·49
1·63	1·45
0·79	0·77
—	1·01
—	0·86
Mean 1·58±0·25	Mean 1·03±0·11

The mean rate of disappearance of galactose was found to be 1.03×10^{-2} min.$^{-1}$. This figure is low compared with the figure for glucose and will closely approximate to the true rate of flow, since there will be no loss by utilization and there is unlikely to be loss by diffusion across the iris.

(B) INDIRECT MEASUREMENT

The blood-aqueous barrier does not behave as an inert membrane but possesses a selective permeability. Each constituent of the aqueous humour crosses the barrier at a rate which is characteristic of that particular compound and is determined by its physico-chemical properties; in other words, each compound enters at its own individual rate. On the other hand, exit from the eye through Schlemm's canal is believed to occur by non-selective bulk flow; that is, all constituents leave at the same rate. In addition to this through-

and-through circulation, there is also a diffusional exchange of water and probably of certain solutes between the aqueous humour and the vitreous body, the lens, and the cornea, and with the blood in the vessels of the iris. The concentration of a given constituent of the aqueous humour in equilibrium with its concentration in the plasma-water is the resultant of its rate of entry and its rate of exit. The relationship between these three variables, rate of entry (k_{in}), rate of exit (k_{out}), and equilibrium ratio (r) can be derived from the fundamental permeability equation:

$$\frac{dC_a}{dt} = k_{in}\, C_p - k_{out}\, C_a, \qquad (1)$$

where the permeability constants k_{in} and k_{out} incorporate all the factors tending to transfer a given substance into, and out of, the aqueous humour; C_a and C_p represent the concentration of a given substance in the aqueous humour and plasma, respectively. At equilibrium:

$$k_{in}\, C_p = k_{out}\, C_a,$$

since

$$\frac{C_a}{C_p} = r \text{ (equilibrium ratio)}$$

$$k_{in} = rk_{out} \qquad (2)$$

It therefore follows that the higher the rate of entry of any compound the lower will be its deficit in the aqueous compared with the plasma-water, when a steady-state has been achieved, until, with rapidly penetrating substances, a rate of entry is attained which equals the rate of exit and the equilibrium ratio becomes unity.

This relationship (equation 2) provided an indirect method of estimating the *rate of flow, for the rate of entry* and the equilibrium ratio can be determined experimentally without disturbing the hydrodynamics of the eye. When a series of compounds is taken, *the minimum value of* k_{out} so obtained will represent the *rate of flow,* for a constituent of the aqueous cannot leave the anterior chamber at a rate *which is lower than the rate of flow.* Unfortunately, there are very few reports of dynamic studies on the aqueous humour which state values for both k_{in} and r. To provide further data, these values have therefore been determined for sucrose, a substance of high molecular weight known to enter the anterior chamber slowly (Davson and Duke-Elder, 1948) and was therefore considered likely to leave the anterior chamber only by flow and not by diffusion, and also for glucose in the diabetic animal where utilization would probably be minimal. Table IV (overleaf) summarizes the results of workers who have used this mathematical approach.

Experimental Methods

(1) Determination of the Rate of Entry and Equilibrium Ratio for Sucrose.—Rabbits weighing 2.0–2.2 kg. were used under pentobarbitone sodium anaesthesia. The general method of suddenly raising the blood concentration by the intravenous injection of 5 per cent. sucrose and removing aqueous samples at suitable intervals (20 and 30 min.) follows that used in previous permeability experiments (Ross, 1951a). The equilibrium ratio was determined by plotting the approach of the concentration in the aqueous humour to that in the plasma at 30-min. intervals until the two curves ran parallel; this

TABLE IV

RATE OF EXIT OF AQUEOUS HUMOUR (k_{out}) DERIVED MATHEMATICALLY FROM RATE OF ENTRY INTO ANTERIOR CHAMBER (k_{in}) AND EQUILIBRIUM RATIO (r)

Reference	Animal	Test Substance	Rate of Exit (per cent. per min.)
Kinsey, Grant, Cogan, Livingood, and Curtis (1942)	Rabbit	Na, Cl	1·4
Kinsey and Grant (1942a, b) ...	Rabbit	Na, Li, Mg, CNS, Cl, Br, urea, fructose	1·4(*a*)—0·6(*b*)
Palm (1948)	Rabbit	$^{32}PO_4$	1·0(*a*)—0·5(*b*)
Harris and Gehrsitz (1949) ...	Rabbit	glucose	2·5
		galactose	3·9
		xylose	4·0
		l-arabinose	2·4
		d-arabinose	2·9
Kinsey and Bárány (1949) ...	Rabbit	*p*-amino hippuric acid	1·43(*a*)—1·13(*b*)
		diodrast	1·22(*a*)—1·02(*b*)
		rayopake	1·25(*a*)—1·10(*b*)
Wilde, Scholz, and Cowie (1947)...	Guinea-pig	^{24}Na	1·6
Langham (1951)	Cat	Cysteine	1·2—2·2
		Ascorbic acid	0·93—1·24
Present paper	Rabbit	sucrose	1·1
	Alloxan diabetic rabbit	glucose	1·1

The two values for k_{flow} given in Col. 4 represent limiting values which result from the method of calculating k_{in}, this being considered to be either by secretion (*a*) or by diffusion (*b*) (Kinsey and Grant, 1942b).

occurred after 5½–6 hours. The renal vessels were ligated during experiments undertaken to determine the equilibrium value but not in those to determine the rate of entry.

Sucrose was estimated by difference after half of each sample had been hydrolysed with 1.27N H_2SO_4 and the glucose estimated by the method of Somogyi (1945).

(2) Determination of the Rate of Entry and Equilibrium Ratio for Glucose in the Diabetic Animal.—The experimental procedure is fully described in Ross (1951b). Rabbits weighing 2.0–2.2 kg. were made diabetic by the intravenous injection of alloxan monohydrate, 300 mg./kg. A week was allowed to elapse after they had become hyperglycaemic before a permeability experiment was performed. The method of determining the rate of entry and the equilibrium ratio was the same as that described for sucrose; pentobarbitone anaesthesia was used and glucose estimated by Somogyi's method.

Results.—The rate of entry of sucrose was found to be 0.23×10^{-2} min.$^{-1}$ and the equilibrium ratio 0.21. In the case of the alloxan-diabetic rabbit the rate of entry was 1.03×10^{-2} min.$^{-1}$ and the equilibrium ratio 0.92. These results, together with those of other workers, are presented in the Figure (opposite) as a graph in which k_{in} is plotted against r. The line is drawn through points of minimal rate of exit and therefore represents the rate of flow, giving a value of 1.1×10^{-2} min.$^{-1}$. It will be noted that several points lie above this line; this is compatible with the hypothesis of an aqueous flow, for such compounds are leaving the eye by diffusion as well as by flow.

Discussion

The fact that all the substances they investigated left the anterior chamber at the same rate led Kinsey and Grant (1942) to postulate that the exit of aqueous humour from the eye is by bulk flow through Schlemm's canal at

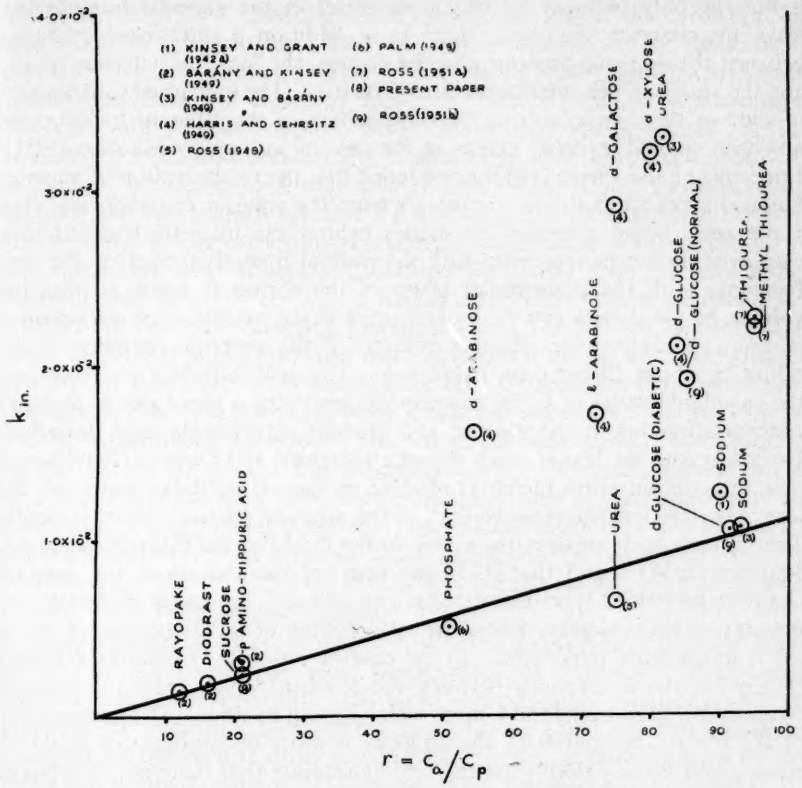

FIGURE.—Relationship between equilibrium ratio (r) and rate of transfer across blood-aqueous barrier (k_{in}) in rabbits, from which k_{out} can be deduced. The line is drawn through the minimum rates of exit (k_{out}) and represents a rate of flow (k_{flow}) of 1.1 per cent. of the volume of the aqueous humour per minute.

Ordinate: Rate of penetration across blood-aqueous barrier expressed as permeability constant k_{in}.
Abscissa: Equilibrium ratio r.

a rate which they calculated to be 1.4 per cent. per min. or 4 cmm. of aqueous humour per min. in the rabbit. This hypothesis necessitated the assumption that 4 cmm. of aqueous humour are formed per minute to replace that lost, with the result that there must be a continuous circulation of fluid from the site of formation, chiefly in the ciliary body, to its site of exit chiefly by way of Schlemm's canal or its homologue. By the use of heavy water, Kinsey, Grant, and Cogan (1942) determined the rate of accumulation of D_2O in the anterior chamber and calculated that there was an exchange of about 20 per cent. of the water of the aqueous humour per minute (= 50 cmm./min. in the rabbit), part of this exchange being with the blood in the vessels of the iris. It follows that drainage through Schlemm's canal

is not the only pathway by which the water of the aqueous humour can leave the anterior chamber; there is in addition a diffusional exchange between the aqueous humour and the cornea, the lens, the vitreous cavity, and the vessels of the anterior surface of the iris. The individual contribution of each of these structures to the composition of the aqueous humour has not been studied in detail except in the case of sodium by Maurice (1951). Friedenwald and Pierce (1932b) concluded that the re-absorption of aqueous humour takes place almost exclusively from the anterior chamber, less than 1 per cent. being absorbed by tissues behind the iris; the method they employed, however, interfered with the normal hydrodynamics of the eye. Exchange with the extracellular water of the cornea is rapid, so that the volume of the cornea can be looked upon as an extension of the aqueous humour, increasing the effective volume of the anterior chamber in the rabbit by about 20 per cent. (Maurice). This will introduce an error into the calculated value of k_{in} in experiments involving a rapid rise in aqueous concentrations as in the glucose and sucrose experiments here described. Exchange with the lens is much slower; Langham and Davson (1949) found that the concentration (activity) of ^{24}Na in the extracellular water of the lens was only 0.6 per cent. of that of the aqueous humour after 24 hours. The vitreous body contributes a little to the fluid flowing through the pupil; Maurice (1951) found that 0.175 per cent. of the sodium in the anterior chamber is derived from the vitreous per minute. Exchange of water, and possibly of some solutes, across the endothelium of the blood vessels of the iris is much more important. In the case of water, the exchange accounts largely for the discrepancy between the 50 cmm. which enter the anterior chamber per minute and the 4 cmm. which leave it by flow. The permeability of the iris to the solutes of the aqueous is more debatable; for instance, Kinsey and Bárány (1949), on the one hand, state that there is no exchange of sodium across the iris whilst Maurice (1951), on the other hand, gives a figure of 0.65 per cent. of the aqueous concentration of ^{24}Na exchanging across the iris per minute.

Although constituents of the aqueous humour can leave the anterior chamber by pathways other than by drainage, the presence of a continuous flow of aqueous humour demands that they cannot leave at a rate which is slower than the rate of flow. The minimum rate of disappearance shown by any of the constituents of the aqueous humour thus gives an indication of the rate of flow and the Figure shows that this corresponds closely to, and cannot exceed, a rate of 1.1 per cent. per minute in the rabbit. It is interesting to note how close to this figure are the results of some of the early workers in this field who employed methods which are now strongly, and rightly, condemned as unphysiological.

Although a value of 1.1×10^{-2} min.$^{-1}$ provides the best fit for the minimum value of k_{out} ($= k_{flow}$) of the various sut ances plotted in the Figure, it will be noted that urea (Ross) falls below the line and has an uncorrected value

of k_{out} of 0.73×10^{-2}. Maurice (1951) points out that if the correction for urea (to allow for penetration into the cornea, vitreous, etc.) is the same as that for ^{24}Na, the corrected value would be 1.1×10^{-2}, which agrees with Kinsey and Bárány's corrected figure of 1.1×10^{-2} min.$^{-1}$ for Rayopake, Diodrast and *p*-amino-hippuric acid. Many and varied values for the equilibrium ratio and permeability constants of urea have been reported; in rabbits, for instance, Kinsey and Grant (1942a) found an equilibrium ratio of 0.66 and a mean value of 1.4×10^{-2} for k_{out}; Kinsey and Robison (1946), using a different chemical technique, reported a value of 0.88 for r, and Kinsey (cited by Kinsey and Bárány, 1949) later gives the remarkably high value of 4.0×10^{-2} for k_{out}. Kinsey and Bárány have expressed the relationship between r and k_{out} graphically as a method of deducing the mode of entry into the eye; this method is based on the argument that, if exit was by flow only, entry would have been by secretion only, whereas if exit was by flow plus diffusion, entry would have been by diffusion with or without super-added secretion. The values for urea (Ross), when plotted on this graph, fall on the line indicating entry by secretion alone; this is surprising, since the slow rate of penetration of urea has been shown to be satisfactorily accounted for on the basis of diffusion of a highly lipoid-insoluble non-electrolyte across a lipoid membrane (Ross, 1951a), and the postulation of the participation of a system for the active transport of urea into the eye is therefore unnecessary.

Direct measurements of the rate of flow based on the rate of disappearance of glucose and galactose give mean rates of 1.58×10^{-2} min.$^{-1}$ and 1.03×10^{-2} min.$^{-1}$ respectively. Owing to the extremely rapid clearance of galactose from the blood, consistent figure for k_{in} and r for this substance could not be obtained in order to compare the rates of flow obtained by the direct and indirect methods. The value of k_{out} for glucose was found to be 1.52×10^{-2} min.$^{-1}$ by the direct method, compared with values per minute of 1.1×10^{-2} in the diabetic rabbit and 2.25×10^{-2} in the normal rabbit by the indirect method. The higher value in the normal animal can be ascribed to loss by utilization.

The presence of a continuous aqueous flow permits the escape from the anterior chamber of a substance whose concentration in the aqueous humour is below that of the plasma; a transfer in the direction aqueous-to-plasma in such circumstances would of course be impossible by any diffusional process. Hidden away in a review on " The present position of the problem of the intra-ocular fluid and pressure ", Duke-Elder and Davson (1948) report experiments by Davson, Duke-Elder, and Maurice, in which inulin (which has a molecular weight of 5,000 and cannot penetrate from the blood into the aqueous humour) was introduced into the anterior chamber by syringe and was found to leave again, even though the inulin concentration of the blood was maintained higher than that of the aqueous throughout the experiment. A similar result was noted in one experiment with galactose

in which the aqueous humour concentration fell from 64 mg./100 g. to 48 mg./100 g. in 60 minutes during which the plasma concentration was 140 mg./100 g. The demonstration of such a movement against a concentration gradient adds further experimental evidence in favour of the idea of the existence of an aqueous flow.

The various modern experimental methods discussed in this paper all agree in giving a minimum rate of exit, or rate of flow, of 1–2 per cent. per min., and reveal the interesting fact that this is irrespective of the species of animal used: that is, irrespective of the volume of the aqueous humour, which ranges from 1.0 ml. in the cat to 0.05 ml. in the chicken, and irrespective also of the chemical used as the test substance, and of any anatomical difference in the architecture of the structures draining the anterior chamber. The development of techniques suitable for the clinical determination of the rate of flow of the aqueous humour in man is becoming of importance in the study of glaucoma but cannot be discussed here; reference may be made to the work of Goldmann (1950) and of Grant (1951) in this connection.

SUMMARY

(1) The experimental evidence in favour of the existence of a continuous circulation of the aqueous through the posterior and anterior chambers of the eye is reviewed.

(2) Previous experimental methods employed to determine the rate of flow of aqueous humour are discussed.

(3) A direct method of estimating the rate of flow without disturbing the hydrodynamics of the eye, by measuring the rate of disappearance of glucose and galactose from the anterior chamber, is described. By this method the rate of flow in rabbits equals 1.58 per cent. per min. of the total volume of the aqueous humour in the case of glucose, and 1.03 per cent. per min. in the case of galactose.

(4) An indirect method of deriving the rate of flow mathematically, from the equilibrium ratio and the rate of transfer of a given substance from the plasma into the aqueous humour, gives a rate of flow of 1.1 per cent. per min., employing sucrose in the normal rabbit and glucose in the diabetic animal.

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BOOK REVIEWS

Individual Differences in Colour Vision. By R. W. PICKFORD. 1951. Routledge and Kegan Paul, London. Pp. 386, 33 figs. 30*s*.

This book contains an account of a vast series of experiments designed to test the extent and distribution of individual differences in colour vision. The work was carried out in the Psychological Department of Glasgow University, and in a period of 8 years more than 1,100 individuals were tested. Many subjects were questioned about their colour experiences in everyday life and about any family history of abnormal colour vision. The object of the research was to design tests applicable to individuals with all types of colour vision, to decide what theory of colour vision would most readily explain the results, and to study the problem of inheritance of colour deficiency.

As the author himself emphasizes in the first chapter, this is a psychologist's book. To the psychologist the sensation is of first importance, just as the physiological mechanism to the physiologist, and the stimulus to the physicist. No one could quarrel with this point of view, but those who attempt to deduce the nature of the physiological basis of colour vision taking the sensations of hue as their foundation (and until recently no other method has been open to those working in the field) are liable to run into a serious difficulty which this author has not completely succeeded in avoiding.

Until we come much nearer to understanding the real relationship between mind and body, any deductions about bodily mechanisms based on sensation—a purely mental phenomenon—can only be extremely tentative. The concept of a " pure " sensation, so important to the psychologist, is, at present, without meaning to the physiologist, to whom the idea that a psychologically pure sensation must result from the activity of a single physiological mechanism is a dangerous fallacy.

In the field of colour vision most psychologists feel that the psychological purity of yellow makes it unlikely that this sensation can arise from the summation of stimulation of red and green receptor mechanisms in the retina. There must be a yellow mechanism. Dr. Pickford feels it desirable that " simplicity of sensation (should be) made to correspond as far as possible with simplicity of receptor system, especially in colour vision ". He sees that this is apparently impossible on the basis of a trichromatic theory, but adds that if it were satisfactory in all other respects this requirement might have to be relinquished. However, the trichromatic theory is not at all satisfactory to him, mainly because of his own researches but also because of other well-known difficulties, such as the necessity for negative coefficients in the fundamental sensation curves at present proposed on the basis of trichromatic matching experiments. He therefore favours some modification of Hering's four-component theory of colour vision. It is not clear whether the psychological purity of white forces him to accept Hering's third (black-white) pair of receptor mechanisms.

This is not the place to discuss the difficulties in accepting the trichromatic theory. It can only be emphasized that, although the theory does not explain all the facts (a failing shared by every colour vision theory) the most serious criticisms usually brought forward can, in the opinion of its adherents, be satisfactorily met. These points are not adequately considered in the first chapter of this book in which several colour vision theories are discussed, a failure which appears to be partly due to a rather naive concept of retinal physiology. It will now be necessary for trichromatists to explain the results of Dr. Pickford's own experiments on a trichromatic basis. He believes that they are not.

There is little doubt that Dr. Pickford's results are valid, or that anyone with the

skill and patience to repeat his experiments would confirm them, but it is questionable whether his is the only possible interpretation.

The new tests were all of the dichromatic matching type ordinarily used for the determination of the Rayleigh equation. They consisted fundamentally of determinations of the amounts of two colours which, when mixed, would match a given standard (*e.g.*, the amounts of red and green required to match a standard yellow, or of blue and yellow to match a standard grey, in both hue and intensity), and these amounts were then compared with the normal values. The results were dealt with on a statistical basis in order to find the range and type of the individual variations.

In discussing his results, Dr. Pickford does not take the possible effect of the yellow macular and other intra-ocular pigments into account. All his variant yellow-blue mixture results could be due to differences in the amount of such pigments, and the fact that all these results fall on a normal frequency-distribution curve also suggests that such an explanation is likely to be correct. Since there is no reason why the depth of pigmentation should be correlated with red or green colour deficiency, one would not expect any necessary association of red or green " weakness " with yellow " weakness ". For "red-green blind" subjects there was a positive correlation. The yellow pigmentation of the ocular media is known to increase with age; unfortunately no correlations of the results with the ages of the subjects are given, but such calculations might provide a clue to the importance of intra-ocular filters in such tests. Until more is known about the normal variation of intra-ocular pigmentation it is doubtful whether the results here reported are in fact at variance with the assumptions of the trichromatic theory.

Finally, a word must be said in praise of the way in which these tests were conducted, especially with regard to the handling of the subjects. Dr. Pickford's remarks on the precautions necessary to prevent a subject, especially if he is colour blind, picking up unintended clues from the experimenter are very much to the point and should be taken to heart by everyone concerned in testing colour vision.

Die Nervenkrankheiten. By G. SCHALTENBRAND. 1951. Georg Thieme Verlag, Stuttgart. Pp. 880, 539 illus. Price .

This considerable text-book of neurology contains much of ophthalmological interest. The whole field of central nervous disease is adequately covered and in consequence many syndromes affecting the eye and its adnexa are described. Among the most useful sections from this point of view are those on cerebral tumours, developmental anomalies, pituitary diseases, endocrine disturbances (wherein exophthalmic disorders are fully described), the muscular dystrophies, and the heredo-degenerative conditions of the central nervous system. The chapters on diseases of the peripheral nerves, organismal and virus infections, and arterial disease, as well as those on central nervous injuries and poisoning, contain a wealth of material in which the ophthalmologist will find himself very much at home. The book is to be recommended both for the clarity of its presentation and for the large number of excellent and informative illustrations. A considerable and representative bibliography is appended.

Diseases of the Fundus Oculi with Atlas. By A. FUCHS. First English ed., 1951. H. K. Lewis, London. Pp. xiv + 337, 81 figs (44 col. pl.). (£8 12*s.* 6*d.*).

This is, in the main, an excellently produced book. The didactic manner of presenting the subject springs from the fact that the book is based on material used for lectures. It contains many statements that would, of necessity, not be endorsed by every ophthalmologist. Being translated from the German, the composition is at times a little stilted and words are used which have a different connotation in Great Britain. For example, it is said that such and such a lesion may be " visualized " where the word " seen " would be more correct.

Every attempt has been made to correlate the microscopic appearances with the ophthalmoscopic findings and this adds very considerably to the interest and usefulness of the book, but one or two of the coloured illustrations are so disappointingly blurred that it is surprising that they were passed for publication.

The fundus pictures are first referred to in the text to illustrate points in the description of a particular disease. There is also a description of each picture set out in a separate section. Nothing could be better than this form of cross-reference and, by looking at the picture first, making up a legend for it, and then comparing that with the printed description, the student can improve his knowledge and powers of observation. While nothing can replace the living fundus as seen with an ophthalmoscope, this book goes very near to performing the impossible.

A Pathology of the Eye. By EUGENE WOLFF. 3rd ed., 1951. H. K. Lewis, London. Pp. 364, 318 figs (5 col. pl.), bibl. (55*s.*).

Eugene Wolff's "Pathology of the Eye" is so well known that a detailed review to introduce the third edition is almost unnecessary; it has now established itself as the outstanding text-book on the pathology of the eye in the English language. The third edition is considerably improved in comparison with its predecessors, the most important addition being the incorporation of over 100 illustrations, many of which are in colour. These illustrations are more than usually good; they are abundant, clear, and admirably illustrate the points in the text. Most of them are photographs of the actual conditions, while the drawings are of unusually high merit. The larger additions to the text in this new edition embrace new work on the origin of pigmented tumours, an excellent description of Schnabel's cavernous atrophy, a review of Coats's disease and retrolental fibroplasia, and the author's original work on the pathology of cysts of the glands of Zeis.

The text is clear, easy to follow, and didactic, and while it does not lose itself in detail or indulge in the discussion of theories, its value is much enhanced by 15 pages of well chosen bibliography.

Ocular Toxoplasmosis. By M. J. HOGAN. 1951. Columbia Univ. Press, New York; Geoffrey Cumberlege, London. Pp. 86, 9 tables, 28 figs, 143 refs. (19*s.*).

In this monograph the literature on toxoplasmosis is critically reviewed in the light of the author's clinical experience and experimental findings. The review is excellent, and may be criticized only for its omissions and not for its factual content. Thus, attention is drawn to the diversity of the clinical manifestations of toxoplasmosis, and it is pointed out that adult infection may be sub-clinical or may present as an acute infection without ocular signs. One feels that more emphasis might have been put upon these features which justify a presumptive clinical diagnosis of toxoplasmosis in cases of adult chorio-retinitis, especially in view of the fact that in 140 cases of uveitis the author found a distribution of toxoplasma antibodies similar to that in his control series.

The experimental work is divided into two parts. In the first, dealing with the treatment of the experimental disease in mice, it is shown that a wide range of chemotherapeutic drugs have failed to effect a cure. The second part describes experimental choroiditis in rabbits following the introduction of toxoplasma into the carotid artery, and it is suggested that the primary lesions occur in the choroidal capillaries.

In a work of such a high general standard it is a pity that some of the photomicrographs are not of the same merit, and that the magnifications are not stated.

The discussion of the laboratory diagnosis of ocular toxoplasmosis is admirable. Attention is drawn to the value and limitations of each test, and the technique of each is described.

Optical Instruments. Proceedings of the 1950 London Conference. 1951. Chapman and Hall, London. Pp. 264. (42*s.*).

Much of this volume of the proceedings of the London Conference on Optical Instruments in 1950 is of considerable interest to ophthalmologists. The opening address by Sir Thomas Merton stresses the debt owed to optics by science, and, indeed, by civilization as a whole. Several of the numerous papers deal with recent developments in optical instruments from the ophthalmic point of view, the most interesting being those on microscopes, phase microscopy, spectrophotometry, photometry, the new types of optical glasses now available in the United States, and plastic lenses.

REVIEWED IN *Ophthalmic Literature*

Documenta Ophthalmologica. Vols V and VI. Multiple authorship. 1951. Junk, The Hague. Pp. 585. (72 guilders).

This volume of *Documenta Ophthalmologica* is made up of the following chapters:

1. Netzhautzysten und zystoide Degeneration der Netzhaut. F. P. Fischer.
2. A case of tritanopy. F. P. Fischer, M. A. Bouman, and J. ten Doesschate.
3. Über den Zuckergehalt der subretinalen Flüssigkeit bei ruptureller Netzhautablösung. F. P. Fischer and R. W. v. Nordheim.
4. "Reefing" of the sclerotic in conjunction with diathermy-coagulation of retinal holes. H. J. M. Weve.
5. Die Polarisation des Himmelslichtes, ihr Sinn und ihre Bedeutung. A. v. Tschermak-Seyssenegg.
6. Essential shrinking of the conjunctiva in a hereditary affection allied to epidermolysis bullosa. A. Sorsby, J. A. Fraser Roberts, and R. T. Brain.
7. Electrical stimulation of the human eye by means of periodical, rectangular stimuli. M. A. Bouman, J. ten Doesschate, and J. v. d. Velden.
8. Stereopsis. H. M. Burian.
9. Growth pressure and metaplasia of conjunctival and corneal epithelium. J. S. Friedenwald.
10. The terminology of the biomicroscopically visible elimination of aqueous humour. K. W. Ascher.
11. Les "sarcomes" de la choroïde. Leur aspects—leur nature—leur origine. J. Nordmann and A. Brini.
12. Abflussdruck, Minutenvolumen und Widerstand der Kammerwasserströmung des Menschen. H. Goldmann.
13. Über die praktische Bedeutung der Blutdruckmessung an der Zentralarterie der Netzhaut. E. Weigelin and H. K. Müller.
14. Some problems of protein chemistry of the eye. A. J. Schaeffer.
15. Spaltlampenmikroskopie und Ophthalmoskopie am Auge von Ratte und Maus. R. Brückner.
16. Pathogénie du glaucome capsulaire. L. Weekers, R. Weekers, and J. Dedoyard.
17. Das Verhalten von Luft und Gasen in Bindehaut, Hornhaut und Vorderkammer. C. Koch.

Since these papers, all of which are of high standard and of more than usual interest, will be reviewed individually in *Ophthalmic Literature* it is not proposed to give them further mention here.

Ophthalmic Nursing. By M. H. Whiting. Sixth Edition, 1951. Churchill, London. Pp. 138, 56 figs. (8*s.* 6*d.*).

The sixth edition of this work, now accepted as a standard for nurses in Gt. Britain, brings its predecessor up-to-date but without introducing radical changes. It might be well in the future if additions were counter-balanced by deletions—if, for example, the cautery puncture operation were offset by the omission of the thermo-cautery which is probably rarely performed nowadays for retinal detachment.

NOTES

OTO-NEURO-OPHTHALMOLOGICAL SOCIETIES

INTERNATIONAL CONGRESS, 1952

THE Seventeenth Meeting of the Societies and International Groups of Oto-Neuro-Ophthalmology will take place at Lisbon and Estoril on April 22 to 26, 1952, under the Honorary Presidency of his Excellency the President of the Portuguese Republic and under the Patronage of the Portuguese Government. Those wishing for further details are requested to apply to the Secretary General of the Congress, Professor Diogo Furtado, Service de Neurologie, Hopital dos Capuchos, Lisbon, Portugal.

UNIVERSITY OF TORONTO

THE Department of Ophthalmology in the University of Toronto has started a glaucoma laboratory in the Banting Institute under the direction of Dr. T. H. Hodgson. This has been made possible by the Ontario Provincial Department of Health from funds provided by federal grant. The laboratory will undertake basic glaucoma studies in conjunction with the glaucoma clinic service; the staff includes Dr. W. P. Callahan, Dr. R. K. MacDonald, and Miss S. Henninghausen, technician.

Plans for a new ophthalmological department have been announced by the Board of Trustees of the Toronto General Hospital, as part of a large expansion programme. This building will be a five-storey structure, containing out-patient eye clinics, consulting rooms, lecture theatres, laboratories, and operation theatres. as well as beds for 75 in-patients.

HOOD MEDAL

THE Hood Medal is presented each year by the Royal Photographic Society for the most meritorious exhibit in any branch of practical photography offered to the Annual Exhibition of the Society.

It may be of interest to our readers that the recommendation this year was that the Medal should be given to the Medical Illustration Department of the Institute of Ophthalmology, which is under the direction of Dr. Peter Hansell, F.R.P.S. It is the first time that the Medal has been awarded for applied medical photography and also the first time it has been presented to a unit and not to an individual.